

**LIFESTYLE-RELATED RISK FACTORS ASSOCIATED WITH ALZHEIMER'S DISEASE:
A SYSTEMATIC REVIEW OF THE LITERATURE**

Mona Hersi

**A thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
in partial fulfillment of the requirements for the
MSc degree in Epidemiology**

**Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa**

© Mona Hersi, Ottawa, Canada 2015

ABSTRACT

In the absence of curative therapies for Alzheimer's disease (AD), primary prevention strategies are imperative. As a component of the National Population Health Study of Neurological Conditions, systematic searches of the literature were conducted to identify lifestyle-related risk factors associated with AD. Results of the overview of reviews was suggestive of an association between current smoking, lower social engagement, light-to-moderate alcohol consumption, higher educational attainment, and regular engagement in physically and cognitively stimulating activities with risk of AD. Results of the de novo systematic review indicated that the available evidence was inadequate to suggest an association between stress (i.e. psychological, work-related) and stress indicators (i.e. PTSD, neuroticism) with risk of AD. Too few studies were identified in the updated systematic review on Mediterranean diet adherence to allow for definitive conclusions. Important methodological limitations preclude the development of public health recommendations for primary prevention initiatives.

ACKNOWLEDGEMENTS

I would like to sincerely thank Drs. James Gomes, Daniel Krewski, and Julian Little for the invaluable opportunity to participate in this study and for offering their time, guidance and expertise along the way. I would also like to extend my appreciation to the many researchers involved in the National Population Health Study of Neurological Conditions for their continuous feedback, to Brittany Irvine for serving as a secondary reviewer, and to Lindsey Sikora for her assistance in developing the search strategies.

I would like to thank my friends and siblings for their encouragement. Most importantly, I would like to extend my deepest gratitude to my parents for always emphasizing the importance of education and hard work. My achievements are a product of their tireless love and support.

TABLE OF CONTENTS

LIST OF TABLES	viii
LIST OF FIGURES	ix
LEGEND	x
CHAPTER 1: INTRODUCTION	1
1.1 Epidemiology	1
1.2 Pathophysiology	1
1.3 Lifecourse perspective.....	2
1.4 Diagnosis.....	3
1.5 Issue.....	5
1.6 Lifestyle risk factors.....	6
1.7 Overview	7
CHAPTER 2: METHODOLOGY	8
2.1 Lifestyle-related risk factors for Alzheimer’s disease: an overview of systematic reviews	8
2.1.1 Objective	8
2.1.2 Literature search strategy	8
2.1.3 Selection Criteria.....	9
2.1.4 Study Selection Method	11
2.1.5 Quality Assessment	11
2.1.6 Data Extraction Strategy	13
2.2 Updating existing systematic reviews or conducting de novo syntheses	14
2.3 Grading the Quality of Evidence.....	17
CHAPTER 3: RESULTS AND DISCUSSION OF THE OVERVIEW OF REVIEWS.....	18
3.1 Literature Search Results	18
3.2 Alcohol	20
3.3 Smoking	37
3.4 Polyunsaturated fatty acids.....	65
3.5 Folate.....	80
3.6 Other micronutrients	88
3.6.1 Vitamin B12	88
3.6.2 Vitamin B-6.....	93
3.6.3 Vitamin B3/Niacin	97
3.6.4 Vitamins C and E	99
3.6.5 Multivitamins	104
3.6.6 Flavanoids	106

3.6.7	Beta-carotene.....	109
3.7	Fruits and Vegetables.....	113
3.8	Caffeine.....	116
3.9	Mediterranean diet.....	124
3.10	Fat intake/Saturated fatty acids.....	131
3.11	Caloric Intake.....	137
3.12	Education.....	140
3.13	Cognitive Leisure Activities.....	149
3.14	Physical Activity.....	156
3.15	Social Engagement.....	175
CHAPTER 4: MEDITERRANEAN DIET ADHERENCE AND ALZHEIMER’S DISEASE: AN UPDATED SYSTEMATIC REVIEW.....		180
4.1	Background.....	180
4.2	Objective.....	181
4.3	Literature search strategy.....	181
4.4	Selection Criteria.....	182
4.5	Study Selection Method.....	184
4.6	Quality Appraisal.....	184
4.7	Data Extraction Strategy.....	184
4.8	Literature Search Results.....	185
4.9	Clinical and methodological characteristics.....	187
4.10	Exposure ascertainment.....	187
4.11	Outcome ascertainment.....	188
4.12	Covariates.....	188
4.13	Quality appraisal.....	189
4.14	Statistical Analysis.....	189
4.15	Study findings.....	193
4.16	Discussion.....	194
CHAPTER 5: PSYCHOLOGICAL STRESS AND ALZHEIMER’S DISEASE: A DE NOVO SYSTEMATIC REVIEW.....		199
5.1	Background.....	199
5.2	Objective.....	202
5.3	Literature search strategy.....	202
5.4	Selection Criteria.....	203
5.5	Study Selection Method.....	204
5.6	Quality Appraisal.....	205
5.7	Data Extraction Strategy.....	206

5.8	Literature Search Results	206
5.9	Clinical and Methodological Characteristics	209
5.10	Exposure ascertainment.....	215
5.11	Outcome ascertainment.....	215
5.12	Covariates.....	216
5.13	Quality Appraisal	216
5.14	Statistical Analyses	219
5.15	Study Findings	219
5.15.1	Prone to Psychological Stress, Neuroticism.....	219
5.15.2	Mid-life Psychological Stress.....	221
5.15.3	Post-traumatic Stress Disorder (PTSD).....	222
5.15.4	Work-related Stress.....	223
5.16	Discussion	226
CHAPTER 6: CONCLUSION.....		232
6.1	SUMMARY	232
6.2	LIMITATIONS	232
6.2.1	Issues relating to the inclusion of existing systematic reviews	233
6.2.1.1	Discordance.....	233
6.2.1.2	Overlap.....	234
6.2.1.3	Quality Assessment	235
6.2.1.4	Publication bias	235
6.2.2	Observational study limitations.....	236
6.2.2.1	Exposure ascertainment.....	236
6.2.2.2	Outcome ascertainment.....	238
6.3	RECOMMENDATIONS AND FUTURE DIRECTIONS	239
REFERENCES.....		242
APPENDICES		281
APPENDIX A-1: Literature Search Strategy		282
APPENDIX A-2: AMSTAR Instrument		292
APPENDIX A-3: Excluded studies (n=444) following full-article screening.....		294
APPENDIX A-4: Excluded Studies (AMSTAR score ≤ 3) (n=39).....		317
APPENDIX A-5: Included Studies (n=27).....		318
APPENDIX A-6: AMSTAR Scoring by Item for Included and Excluded studies		321
APPENDIX A-7: Systematic reviews included in the National Population Health Study of Neurological Conditions (n=81)		340
APPENDIX B-1: Literature Search Strategy.....		345
APPENDIX B-2: Excluded studies (n=68) following full-article screening.....		351

APPENDIX C-1: Literature Search Strategy.....	357
APPENDIX C-2: Newcastle-Ottawa Scale	364
APPENDIX C-3: Excluded studies (n=22) following full-article screening.....	366
APPENDIX C-4: Included Studies (n=9).....	368

LIST OF TABLES

Lifestyle risk factors associated with AD: an overview of systematic reviews

Table 1 - Alcohol and risk of AD.....	32
Table 2a - Smoking and risk of AD	57
Table 2b - Overlap across reviews reporting on smoking and risk of AD	63
Table 3 – Polyunsaturated fatty acids (PUFAs) and risk of AD	74
Table 4 – Folate and risk of AD	86
Table 5 – Vitamin B-12 and risk of AD.....	91
Table 6 – Vitamin B-6 and risk of AD.....	95
Table 7 – Vitamin B-3/Niacin and risk of AD	98
Table 8 – Vitamins C and E and risk of AD	102
Table 9 – Multivitamin use and risk of AD.....	105
Table 10 – Flavonoids and risk of AD	108
Table 11 – Beta-carotene and risk of AD.....	111
Table 12 – Fruit and vegetable consumption and risk of AD	115
Table 13 – Coffee/Caffeine consumption and risk of AD.....	122
Table 14 – Mediterranean diet and risk of AD.....	129
Table 15 – Saturated, transunsaturated, and total dietary fat and risk of AD.....	135
Table 16 – Caloric intake and risk of AD	139
Table 17 – Educational attainment and risk of AD	146
Table 18 – Cognitive leisure activities and risk of AD	154
Table 19 – Physical activity and risk of AD	171
Table 20 – Social engagement and risk of AD.....	179
Table 21 - Characteristics and findings of the included studies.....	190
Table 22 - Characteristics and findings of the included studies.....	210
Table 23 - Quality appraisal of cohort studies according to Newcastle-Ottawa Scale [§]	218
Table 24 - Quality appraisal of case-control studies according to Newcastle-Ottawa Scale [§]	218

LIST OF FIGURES

Lifestyle risk factors associated with AD: an overview of systematic reviews

Figure 1 – Decision tool for deciding on an updated review or de novo synthesis 16

Figure 2 - PRISMA Flow Diagram: Overview of Systematic Reviews 19

Figure 3 - PRISMA Flow Diagram: Updated Systematic Review 186

Figure 4 - Forest plot of available studies on Mediterranean diet adherence and risk of AD 194

Figure 5 - PRISMA Flow Diagram: De Novo Systematic Review 208

Figure 6 - Forest plot of available studies on psychological stress and AD 225

LEGEND

A β	Amyloid beta
ACTH	Adrenocorticotrophic hormone
AD	Alzheimer's disease
AHRQ	Agency for Healthcare Research and Quality
ALA	Alpha-Linolenic acid
AMSTAR	Assessment of Multiple Systematic Reviews
APOE	Apolipoprotein E
CI	Confidence interval
CRF	Cortisol releasing factor
DHA	Docosahexaenoic acid (DHA)
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPA	Eicosapentaenoic acid
FFQ	Food frequency questionnaire
HPA	Hypothalamic-pituitary-adrenal
HR	Hazard ratio
HTA	Health Technology Assessment
ICD	International Classification of Diseases
ISF	Interstitial fluid
JC	Job control
JD	Job demands
JS	Job strain
meSH	Medical subject heading
NFT	Neurofibrillary tangle
NHCC	Neurological Health Charities Canada

NINCDS- ADRDA	Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders Association
NOS	Newcastle-Ottawa Scale
OR	Odds ratio
PHAC	Public Health Agency of Canada
PUFA	Polyunsaturated fatty acids
PTSD	Post-traumatic stress disorder
RR	Relative risk
SS	Social support
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Epidemiology

According to the Public Health Agency of Canada, Alzheimer's disease (AD) is the most common form of dementia.¹ Although dementia and AD are age-related conditions, they are not considered to be typical of the normal aging process.^{2,3} Dementia is a clinical syndrome characterized by "memory impairment and at least one of the following: aphasia, apraxia, agnosia, or a disturbance in executive functioning".⁴ Dementia is characteristic of a number of conditions including, but not limited to, AD.^{5,6} AD involves irreparable neuronal degeneration which gives rise to a myriad of clinically detectable impairments.^{7,8} Short- and long-term memory loss serve as the most pronounced cognitive marker of AD while non-cognitive indicators encompass declining physical capacity and alterations in behaviour.^{8,9} Characterized by debilitating symptoms which can dramatically impact quality of life, AD usually results in death within a decade post- diagnosis.⁹

One in ten elderly Canadians had dementia in 2011 and approximately 60-70% of these cases were attributed to AD.⁹ There is consistent evidence to suggest that the incidence rates of AD increases with age.¹⁰ Incidence rates increase by 0.5% per year between age 65 to 70 and by 6 to 8% after age 85.¹⁰ Compared to figures estimated in 2008, a more than two-fold increase in AD incidence (103 700 to 257 800) and prevalence (480 600 to 1 125 000) is anticipated by 2038.¹¹ In 2008, the economic cost of AD was estimated at \$15 billion, a figure expected to increase ten-fold by 2038 (\$153 billion).¹² With an aging Canadian population, it is forecasted that by 2038, dementia will constitute as the "the highest economic, social, and health cost burden of all diseases in Canada".⁶

1.2 Pathophysiology

Neuropathological evidence of AD requires the presence of amyloid plaques and neurofibrillary tangles.^{13,14} According to the amyloid cascade hypothesis, the pathogenesis of AD involves the development of amyloid plaques.¹⁴ Briefly, amyloid precursor protein gives rise to amyloid β ($A\beta$), the primary component of amyloid beta plaques responsible for neuronal damage in AD.¹⁴ While the particular mechanism of $A\beta$ -initiated neuronal damage remains largely elusive, several hypotheses have been proposed.¹⁵ The detrimental effect of $A\beta$ has been attributed to its

putative neurotoxic effects as well as its ability to trigger inflammation and oxidative stress, factors implicated in AD pathology.¹⁵

The amyloid cascade hypothesis also attempts to explain the mechanism leading to the development of the second indicator of AD, neurofibrillary tangles (NFT). It postulates that the formation of NFT, from a protein referred to as “tau”, is a response to an influx of A β .¹⁴ In vivo research supports this hypothesis as “tau pathology [was] accelerated....by A β deposition”.¹⁵ However, the validity of the amyloid cascade hypothesis has been questioned and further research is required to attain a better understanding of the relationship between A β and tau and their contribution to the pathogenesis of AD in general.^{14,15} It is important to note that mitochondrial dysfunction has been implicated in the pathophysiology of AD and is believed to initiate the development of beta-amyloid plaques and NFTs.¹⁶

Additional features of AD pathophysiology include neuronal and synaptic loss.¹⁷ Synaptic loss has proven to be more closely related to the clinical manifestation of AD (i.e. cognitive impairment) when compared to both amyloid plaques and neurofibrillary tangles.¹⁷

1.3 Lifecourse perspective

The lifecourse perspective postulates that AD is a result of exposure to detrimental factors across the lifespan.¹⁸ Neuropathological changes associated with AD are believed to begin several decades before symptoms can be detected.¹⁸ Neuropathological correlates of AD have been observed as early as the second decade of life.¹⁸ However, the clinical expression of AD typically occurs in late-life.¹⁸

While the impact of genetic predisposition cannot be overlooked, exposures encountered throughout the lifespan may also influence etiology.¹⁸ Several early-life factors have been implicated in the development of AD. Early-life obesity, for example, may predispose individuals to chronic diseases such as diabetes and hypertension, both of which are putative risk factors for AD.¹⁸ Parental socioeconomic status is believed to impact several factors, all of which may play a role in AD risk.¹⁸ These factors include offspring nutritional status, educational achievement, and future socioeconomic status. In particular, early-life nutritional status is imperative for brain development which in part, impacts cognitive reserve.¹⁸

In midlife, vascular (e.g. hypertension, hypercholesterolemia, diabetes, etc.) and lifestyle (e.g. smoking, physical activity, etc.) factors have been implicated in the development of dementia.¹⁹ In late-life, social support, access to health care, and co-existing diseases are putative factors involved in the etiological process.¹⁹ Certain factors may impact disease development in all stages of

life.¹⁹ For example, socioeconomic status in early-, mid, and late-life is believed to impact risk of AD and dementia.¹⁹ Other factors may exert a differential effect depending on the timing of “exposure”.²⁰ For example, obesity in mid- but not late-life appears to increase risk of AD and dementia.²⁰

Exposures acquired across the lifespan may directly impact the neuropathological process of AD.¹⁸ Alternatively, certain factors may delay the clinical expression of the disease by increasing cognitive reserve.¹⁸ The concept of cognitive reserve, as it relates to education, physical activity, and cognitively stimulating activities is described in further detail in Chapter 3.

1.4 Diagnosis

A definite diagnosis of AD can only be confirmed following post-mortem examination; however, several criteria have been developed to diagnose cases of possible or probable AD in living subjects.^{15,21,22,23} Widely accepted criteria for the clinical diagnosis of AD include the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR), the Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA), and the World Health Organization’s (WHO) International Classification of Diseases (10th revision, ICD-10).^{22,23}

Developed in 1984, the original NINCDS-ADRDA criteria for probable AD requires evidence of gradual disease progression in the absence of other brain disorders.²² However, a diagnosis of definite AD requires clinical and histopathological evidence.^{22,24} Advancements in AD research warranted an update of the original NINCDS-ADRDA criteria.¹⁷ Recent publications from the working group, convened in 2009, outline the revisions to the original criteria.¹⁷ Briefly, notable changes to the NINCDS-ADRDA criteria include: (1) differentiation between the “pathophysiological process” of AD and the clinical manifestation of the disease, (2) criteria for distinguishing between AD and non-AD dementias, (3) addition of two classes of biomarkers (biomarkers of A β elevation and neuronal damage) for diagnostic purposes, and (4) the development and “formalization of different stages of disease”.¹⁷ To reduce the occurrence of disease misclassification error in epidemiological studies, the use of sensitive and specific criteria for outcome ascertainment is of paramount importance.²⁵ In comparison to the most rigorous method for AD ascertainment, namely post-mortem neuropathologic examinations, studies have suggested that the NINCDS-ADRDA “has fair sensitivity (49-100%) and specificity (47-100%)” for the

diagnosis of probable AD.²⁶ The sensitivity (85 to 96%) but not specificity (32 to 61%) indexes are said to be higher for diagnoses of possible AD.²⁶

According to the DSM-IV-TR criteria, a positive diagnosis of AD necessitates cognitive impairment and memory deficits.²² Both the ICD-10 and DSM-IV criteria distinguish between early and late onset cases and both attempt to exclude other conditions which may explain symptomology (e.g. substance abuse, other neurological disorders).^{23,24} All three diagnostic criteria emphasize the importance of gradual onset as an inclusionary criterion.²⁴

Several limitations of the available clinical diagnostic criteria have been noted. An important limitation involves the reliance on subjective judgement.²⁴ The subjectivity is rooted in the “lack of operationalization” (i.e. definitions and guidelines) of the NINCDS-ADRDA, ICD-10, and DSM-IV criteria.²⁴ With respect to the NINCDS-ADRDA criteria, subjectivity is reflected in the “low to moderate” interrater reliability reported in the literature.²⁷ The issue of misdiagnosis must also be raised. Studies with histopathologic evidence suggest that Parkinson’s disease is most commonly misdiagnosed as AD antemortem.²⁴

The lack of objective measures to detect pathophysiology antemortem has been cited as an important limitation.²⁸ The revised NINCDS-ADRDA has addressed this limitation by including biomarkers (i.e. “fluid and imaging measures”) indicative of AD pathophysiology (i.e. atrophy, elevations in both amyloid beta and CSF tau, etc.) as a component of the diagnostic process.¹⁷ The addition of biomarkers is believed to not only aid the clinical diagnosis of AD, but also the detection of pre-clinical dementia, which due to the absence of symptomology, is undetectable using clinical diagnostic criteria.^{17,28} This constitutes an important advancement as biomarkers enable earlier disease detection.²⁸ While biomarker analysis represent a step forward, validation and standardization of the biomarkers are needed.¹⁷ With respect to standardization, acceptable thresholds for the “continuous” biomarker data (i.e. “clearly normal, clearly abnormal, and perhaps intermediate”) need to be developed.¹⁷

The inability to adequately differentiate between dementia subtypes, particularly between AD and frontotemporal dementia, is also a limitation of the previous version of the NINCDS-ADRDA.^{24,27} As noted by the working group, advancements in research with respect to “distinguishing features” across dementia subtypes have enabled improvements to the criteria.²⁹ The revised NINCDS-ADRDA has incorporated explicit exclusionary criteria for subtypes such as frontotemporal dementia and dementia with Lewy bodies.²⁹

Advancements in AD research have also necessitated the update of the 1997 National Institute on Aging/Reagan Institute of the Alzheimer Association Consensus Recommendations for the Postmortem Diagnosis of AD (NIA-Reagan criteria).³⁰ Prior to the update, the 1997 version

served as the “most current guidelines”.³¹ As there now evidence to suggest that neuropathology may not directly correlate with clinical manifestation of AD, the newly revised neuropathological criteria no longer require antemortem evidence of dementia.³⁰ The new criteria also provide detailed guidelines for the identification of histopathological evidence of “co-existing” diseases (e.g. Lewy body disease, cerebrovascular disease, etc.).³⁰ Further, the consideration of biomarker and genetic findings in the diagnostic process was also introduced.³⁰ While the revised criteria are in keeping with advances in research, the subjectivity associated with previous criteria remains a limitation.³²

1.5 Issue

Despite the abundance of Alzheimer’s disease research, the etiology of the disease is not yet understood.⁶ To date, a number of risk factors for AD have been identified including age, family history, mild cognitive impairment, and smoking.⁶ In a recent search of the literature aimed at identifying observational studies investigating potential risk factors for the development of AD, a total of 4350 potentially relevant citations were identified. In an effort to synthesize this evidence, a number of these observational studies have been incorporated into existing systematic reviews. A search restricted to systematic reviews and meta-analyses yielded 667 potentially relevant citations. This large number of retrieved records is reflective of the “explosive growth in the number of systematic reviews and meta-analyses” being published.³³ As a rapidly developing field of research, providing a concise report on risk factors associated with AD etiology is imperative for guiding primary prevention efforts, clinical decision-making, informing health care policy, and ultimately reducing disease incidence.

The need to identify and synthesize the available evidence has been identified as an objective of the National Population Health Study of Neurological Conditions commissioned by the Public Health Agency of Canada (PHAC) and the Neurological Health Charities Canada (NHCC). As a component of this expansive project, the objective of the present study was to provide a comprehensive synthesis of risk factors associated with AD. Ultimately, the incidence, severity and disabling nature of AD, as well as the extensive economic and social costs attributed to this neurological condition, warrant the systematic and comprehensive search and summary of etiological risk factors associated with the disease.

1.6 Lifestyle risk factors

Risk factors can be divided into two distinct categories: modifiable factors and immutable factors. While the identification of immutable factors provides insight into disease etiology, their non-modifiable nature precludes primary prevention efforts. Alternatively, identification of modifiable factors involved in the causal pathway can spearhead individual- and population-level interventions to address these factors and ultimately mitigate AD risk. Despite advancements in AD research, currently, there are no available curative therapies for AD.³⁴ Consequently, primary prevention by targeting modifiable factors might confer the most pronounced public health impact.³⁴

Research suggests that the adoption of risk-reducing lifestyle behaviours such as mental stimulation, physical activity, and consuming a low fat diet may serve as components of a primary prevention strategy for AD.³⁵ While lifestyle-related factors may encompass a small number of all putative modifiable factors, integration of risk-reducing behaviours and avoidance of detrimental factors serve as relatively straightforward interventions adoptable at the individual level. Further, there is research to suggest that modifiable risk factors may account for a considerable proportion of AD cases globally.³⁶ One systematic review examined the population attributable risk of several modifiable risk factors (i.e. “diabetes, mid-life hypertension, midlife obesity, smoking, depression, low educational attainment, and physical inactivity”).³⁶ Relative risks were estimated by meta-analysis. Considered cumulatively, these factors appeared to account for “half of AD cases globally (17.2 million) and in the US (2.9 million).”³⁶ Considered individually, the study found that 13%, 14%, and 19% of global cases of AD are attributed to physical inactivity, smoking, and low levels of education, respectively. It estimated that approximately 1 to 1.4 million global cases of AD would be avoided by decreasing smoking, physical inactivity, or low educational attainment by 25%. In the US alone, a 25% reduction in low educational attainment, smoking, and physical inactivity would avoid 91 000, 130 000, and 230 000 cases, respectively.³⁶ It is important to exercise caution when interpreting the derived estimates as PAR “assumes that there is a causal relation...”³⁶ While these variables may be associated with AD, causation cannot be established based on the available observational evidence.³⁷ Also, only a few of several putative lifestyle-related factors were considered.³⁶

As the only available means for preventing the onset of AD, the focus of this body of work was to identify modifiable factors, namely lifestyle-related factors or “...patterns of living that [an individual chooses] to follow”³⁸ which are associated with risk of developing AD. While modifiable, chronic illnesses such as hypertension and diabetes mellitus are secondary to or in part a result of primary lifestyle factors such as physical activity levels and dietary choices.^{39,40,41} These and other

putative risk factors for AD (i.e. environmental, genetic, biological, pharmacological, etc.) have been reviewed separately for the National Population Health Study of Neurological Conditions and will not be described herein.

The study of lifestyle risk factors primarily relies on findings from observational studies which are susceptible to several sources of bias. In particular, the potential for reverse causation poses a particular challenge. Presence of preclinical dementia or AD may alter exposure status.⁴² Those with preclinical AD or dementia may, for example, reduce the frequency at which they participate in cognitive leisure activities due to the onset of memory and cognitive deficits.⁴² Studies which fail to adequately exclude participants with preclinical dementia are susceptible to bias due to reverse causation.⁴² Other important methodological issues are presented throughout the report and further summarized in Chapter 6.

1.7 Overview

This study is designed to answer several questions pertaining to the etiology of AD. According to Whitlock et al., unlike traditional systematic reviews, reviews attempting to “evaluate a number of linked clinical questions, multiple interventions or diagnostic tests, different or distinct population groups, and/or many outcomes” are considered “complex reviews”.³³ Since the study is aimed at answering a number of related questions, more specifically, the role of *several* lifestyle-related risk factors on AD, the current study is considered a complex review. Although systematic reviews traditionally involve a review of original studies, the incorporation of existing systematic reviews and meta-analyses in complex reviews is common and avoids duplication of existing work.³³ The thesis consists of three components: (1) an overview of existing systematic reviews, (2) an update to an existing systematic review, and (3) a *de novo* systematic review of an etiological risk factor that has not been considered in an existing systematic review.

Briefly, for the preliminary phase of the complex review, a systematic search of the literature was conducted to identify and synthesize evidence from existing systematic reviews. The preliminary phase was also integral for identifying gaps in the available systematic review literature and for informing the second and third phases of the thesis which involved an update of an existing systematic review on Mediterranean diet adherence and a *de novo* systematic review on stress and stress indicators.

CHAPTER 2: METHODOLOGY

2.1 Lifestyle-related risk factors for Alzheimer's disease: an overview of systematic reviews

2.1.1 Objective

The objective of the preliminary phase of the complex review was to identify lifestyle-related risk factors for Alzheimer's disease through a systematic and comprehensive search of the literature.

2.1.2 Literature search strategy

A search strategy designed to locate systematic reviews was developed by the lead reviewer in consultation with an information specialist. The search strategy was developed in the MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations databases. The search strategy was comprised of keywords and MEDLINE controlled vocabulary or "medical subject headings" (meSH) relating to three concepts: disease terminology, risk/risk factor terminology, and review terminology. Keywords and mesh terms within each concept were combined using the BOOLEAN operator "OR" while the concepts themselves were combined using the BOOLEAN operator "AND". A methodological filter was applied to identify systematic reviews and meta-analyses while eliminating studies with alternate methodological designs. A second filter was incorporated to restrict the search to studies examining etiological risk factors. The search was further limited to humans and to studies published in English and French as resources for translating foreign language studies were unavailable. The search strategy developed in OVID MEDLINE served as a template for the development of search strategies tailored to other databases. In alternate databases, the search strategy retained its structure; however, database-specific medical subject headings and filters were applied to ensure compatibility.

Based on recommendations by Whitlock et al., "higher-yield" bibliographic databases for systematic reviews, such as the Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects (DARE) were also searched.³³ To maximize the comprehensiveness of the search, additional databases including PubMed, EMBASE, CINAHL, HuGENET, PsychINFO, TOXNET Toxicology Data Network and AARP Ageline were searched to identify systematic reviews. Data was also abstracted from the AlzGene database to supplement the search for genetic variants associated with AD. The initial search was conducted in September 2011. The

OVID AutoAlerts feature was enabled to ensure that newly indexed relevant articles were received through email notification. The AutoAlerts feature was disabled on December 31, 2011. Databases lacking an AutoAlerts feature were re-searched until the end of December 2011. Therefore, the study should have captured all relevant systematic reviews indexed in the searched databases up to December 31, 2011.

The tendency for studies reporting positive findings to be published more often than studies reporting negative findings may give rise to publication bias.⁴³ To minimize the potential for publication bias, the grey literature was searched to identify unpublished systematic reviews. The grey literature search involved a search of the ProQuest Digital Dissertations and Theses database, an internet search of Google and GoogleScholar, and the search of disease-specific journals, namely, the *American Journal of Alzheimer's Disease and Other Dementias* and the *International Journal of Alzheimer's Disease*. In addition, the reference lists of important articles were handsearched to identify relevant systematic reviews. Refer to Appendix A-1 for the grey literature and database specific search strategies.

2.1.3 Selection Criteria

Studies identified from the database and grey literature searchers were exported from the databases into a reference management software package (Reference Manager, version 10.0; Thomas Reuters; New York, NY). Once imported into Reference Manager 10.0, the retrieved articles were then imported into DistillerSR, an internet-based screening and data extraction tool (DistillerSR, Evidence Partners, Ottawa, Canada) for the screening and data extraction processes. Briefly, DistillerSR was organized into a number of “levels”. A two-tiered approach was adopted for the screening process. The title and abstracts of the identified studies were screened in the first of the two screening levels. Based on the review of the title and abstract, relevant studies were retained for further examination in the secondary screening level while studies failing to satisfy the eligibility criteria were excluded. In the event that a study’s relevancy was unclear based on a review of the title and abstract alone, the study was retained for further examination in the secondary screening level. The entire publication was reviewed to ascertain relevancy in the secondary screening level. The eligibility of a given study was determined according to adherence to a priori established selection criteria pertaining to the population, exposure, outcome, and study design.

Studies were eligible for inclusion if the following inclusion criteria were satisfied:

- **Population:**“(1) Humans, (2) Adults”²⁰
- **Exposure:** Risk factors/exposures associated with the development of Alzheimer's disease
- **Outcome:** Diagnosis of Alzheimer's disease
- **Study Design:** Systematic reviews. For the purpose of this study, the following operational definition of a systematic review was adopted: “a systematic, explicit, [comprehensive], and reproducible method for identifying, evaluating, and synthesizing the existing body of completed and recorded work produced by researchers, scholars, and practitioners”.⁴⁴ To ensure that the review is reproducible, databases searched and the inclusion/exclusion criteria used to establish relevancy must be explicitly stated.⁴⁵ Based on the definition, specific criteria were developed to distinguish systematic reviews from literature reviews. More specifically, for the purpose of this study, a literature review was considered to be systematic in nature if it adhered to the following criteria: (1) must indicate that a computerized literature search was conducted, (2) must explicitly state the inclusion and/or exclusion criteria used.
- **Time period:** All years up to December 31, 2011
- **Publication languages:** French and English studies

Systematic reviews and meta-analyses were excluded from the review if:

- The study examined etiological risk factors for cognitive decline, Mild Cognitive Impairment or non-AD dementias (e.g. Frontotemporal dementia, Pick's disease, Lewy body dementia, vascular dementia, Creutzfeldt-Jakob disease)
- The study failed to distinguish AD from all-cause dementia or dementia subtypes (i.e. risk estimates not reported for AD)
- The study employed an alternative methodological design (e.g. observational studies, randomized controlled trials, narrative reviews, case-studies, editorials, expert opinions, etc.)
- The study focused on prognostic risk factors or therapeutic approaches
- The report was not conducted in human subjects
- The report did not adhere to our definition of a systematic review:

- The study failed to specify that a computerized search was conducted (i.e. included studies were not identified using a systematic search of databases)
- A priori established inclusion/exclusion criteria were not explicitly stated or were vague(e.g. reviews that simply state that “all studies relevant to the exposure and outcome were included” or “all English language studies were included”)
- Reports was written in a language other than English or French
- Entire publication could not be obtained

2.1.4 Study Selection Method

To minimize the biased inclusion of studies, screening was conducted independently by two reviewers. The “liberal accelerated” duplicate screening process, employed in the conduct of systematic reviews by the Ottawa Methods Center, was used in this study.⁴⁶ Briefly, only studies that were deemed irrelevant and consequently eliminated by the lead reviewer underwent independent review by a secondary reviewer. The liberal accelerated method was employed to reduce the number of articles that required duplicate screening resulting in a more efficient use of resources.⁴⁶ In the event of discordance between reviewers, the study in question was re-examined by both reviewers and a decision was reached through consensus. Studies that adhered to the selection criteria advanced to the quality assessment phase of the review.

Based on recommendations, the DistillerSR screening levels were piloted by both the lead and secondary reviewer on a sample of 5 systematic reviews prior to study onset.⁴⁷ A record of screening for both levels was maintained in DistillerSR where a weighted Cohen’s Kappa coefficient was computed to measure the inter-rater agreement. A minimum Cohen’s Kappa statistic of 0.61 – 0.80, indicating “substantial agreement”, was required to consider the pilot screening successful.⁴⁸ A weighted Cohen’s Kappa of 0.77 was achieved.⁴⁸

2.1.5 Quality Assessment

According to recommendations put forth by Whitlocke et al., assessing the quality of existing systematic reviews is of paramount importance when attempting to incorporate existing systematic reviews in a given review of the literature.³³ To minimize the potential for bias, Whitlocke et al. recommends that inclusion should be restricted to higher-quality systematic

reviews.³³ Despite the subjectivity associated with quality assessment tools, Whitlock et al. recommends the use of the Assessment of Multiple Systematic Reviews (AMSTAR) tool for evaluating the quality of existing systematic reviews.³³

The AMSTAR instrument (Appendix A-2) is a checklist composed of 11 criteria.⁴⁹ Briefly, the AMSTAR instrument considers the thoroughness of the search strategy, susceptibility to bias, and the appropriateness of the statistical techniques used to meta-analyze the data.⁴⁹ To receive a point for the first item of the AMSTAR instrument, reviewers must have indicated the objective of the review and they must have stated the a priori established inclusion criteria used for assessing relevancy. A point was assigned for the second item of the instrument if the study screening and data extraction processes were conducted independently by at least two reviewers and if a consensus procedure was specified for disagreements for the screening and/or data extraction phases. A point was not provided if extraction was conducted by one reviewer and verified by another. A review received a point for the third item if a comprehensive search of the existing literature was conducted to identify relevant studies. Each of the following criteria had to be satisfied to receive a point for the third item: (a) search of more than one database, (b) databases searched and years included in the search strategy explicitly stated, (c) keywords or MeSH terms used in the search strategy specified, (d) search strategy provided, and (e) search was “supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the field, and by reviewing the references in the studies found”.⁴⁹ To receive a point for the fourth item, reviewers had to specify reasons for exclusion (i.e. on the basis of language or publication status) and that “they searched reports regardless of publication type”.⁴⁹ The latter criterion required reviewers to report that the grey literature was searched to identify unpublished studies. A point was assigned for the fifth and sixth criteria if a list of included and excluded studies was provided and if the characteristics of the included studies were summarized in an evidence table, respectively. However, in order for a point to be assigned for the sixth item, the evidence table must have included data pertaining to the participants, interventions, and outcomes of the included studies. In order to earn a point for the seventh item, studies must have been quality assessed. A point was allocated for the eighth item if subgroup analyses based on methodological quality were conducted and/or the methodological limitations of the included studies were taken into account when deriving conclusions. If a meta-analysis was conducted, a point was assigned for the ninth item if heterogeneity was assessed and if appropriate methods were employed to address the heterogeneity (e.g. random effects method was utilized or a pooled analysis was relinquished altogether). If the reviewers assessed publication bias, a point was assigned for item 10. Lastly, in order to earn a point for the eleventh item of the

AMSTAR tool, the reviewers had to disclose any conflicts of interest. In addition, the funding sources of the included studies had to be specified in the review.

Points assigned to each item were combined and a total AMSTAR score was derived. Reviews were then categorized as high, moderate, or low quality according to the thresholds employed by the Canadian Agency for Drugs and Technologies in Health (CADTH). Reviews with a total score ranging from 0 to 3 were deemed to be of low methodological quality, those scoring 4 to 7 points were considered moderate-quality reviews, and high quality reviews required 8 to 11 points.⁵⁰

The AMSTAR quality assessment tool was piloted on five studies by both reviewers prior to the onset of the study. To ensure that the quality assessment process was standardized, the total score assigned to each of the five studies included in the piloting process were compared. Because the use of the AMSTAR tool requires “subjective judgment”, a successful pilot testing of this tool required that both reviewers rate the study as the same quality category rather than assigning the same numerical score.⁴⁹ The same quality category was assigned by both reviewers for all five studies included in the piloting process.

To minimize the subjectivity of the quality assessment process, quality assessment was conducted by two independent reviewers. However, due to limited resources, duplicate quality assessment was only feasible for a randomly selected, 10% sample of studies. In the event of discordant scoring between the reviewers, consensus was achieved through discussion. Only moderate and high quality reviews were eligible for inclusion. All low quality reviews were excluded from the complex review.

2.1.6 Data Extraction Strategy

Data extraction of moderate and high quality systematic reviews was conducted in DistillerSR. The extraction process was divided into three levels. Each level was composed of an a priori established, standardized data extraction form. Data pertaining to the study populations, methodology, and results were collected. Abstracted population variables included sex, age, co-morbidities, race, country of origin, type of AD, and the severity and duration of the disease. Methodological variables included the exposure under study, the setting of the included studies (e.g. community-, population-, or institution-based studies), study design (e.g. cohort, case-control, etc.), the inclusion/exclusion criteria of the review, databases and years searched, elements of the search strategy (e.g. meSH terms and keywords), and the quality assessment instruments used. With respect

to the results of the review, results of the pooled analysis, subgroup analyses, and tests for publication bias were extracted. For reviews without a meta-analytic component, risk estimates from included primary studies were presented. Conclusions drawn by review authors were summarized and reported.

The data extraction process was conducted by the lead reviewer. To minimize the potential for bias, a second reviewer was responsible for extracting data from a randomly selected 10% sample of studies. In the event of discordant data collection, consensus was established through discussion.

2.2 Updating existing systematic reviews or conducting de novo syntheses

Existing reviews of high methodological quality present a low risk of bias and thus do not require a de novo synthesis.⁵¹ However, despite the methodological rigor of high-quality reviews, the validity of their findings may be compromised if the reviews are out of date.⁴⁵ To ensure that high quality reviews remain valid, they must be updated with newly emerging evidence.⁴⁵ According to Moher et al., an update of a systematic review is defined as “...a discrete event with the aim to search for and identify new evidence to incorporate into a previously completed systematic review”.⁴⁵ An update requires that the original protocol of the existing review be “retained” and replicated.⁴⁵ The aim is to identify new evidence which has not been captured in an existing review.⁴⁵ Broadening the scope of the original search strategy by searching additional bibliographic databases can be considered an update of an existing systematic review.⁴⁵ Similarly, attempting to identify evidence which has emerged after the completion of an existing systematic review also constitutes an update.⁴⁵ Moher et al. suggest that an attempt to identify new evidence is considered an update even if the attempt does not yield novel evidence.⁴⁵

A brief decision tool was developed to allow for a systematic approach in deciding whether an existing systematic review was eligible for an update (Figure 1). Reviews rated to be of high methodological quality satisfied the first criterion for an update. In addition to receiving a “high” score on the AMSTAR tool, existing reviews had to also satisfy three a priori criteria: duplicate screening, duplicate data extraction, and quality assessment of the included studies.⁵² Although duplicate screening and data extraction are widely recommended, limited resources often necessitates independent, duplicate screening and extraction of only a sample of studies. As such, partial duplicate screening and extraction were considered permissible. High quality reviews failing to satisfy the criteria were ineligible for an update and necessitated a de novo systematic review.

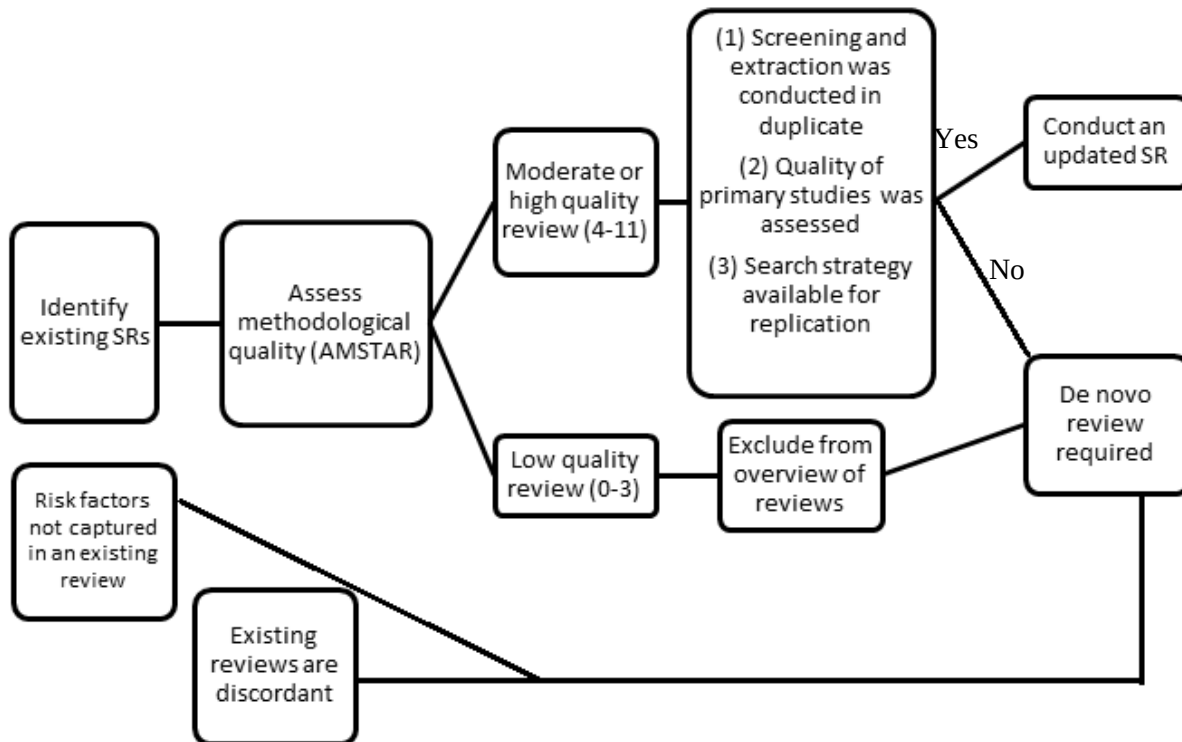
De novo systematic reviews were warranted if any of the following were satisfied: (1) existing systematic reviews were of poor or moderate methodological, (2) high quality reviews did

not conduct duplicate screening/extraction and/or quality assessment of primary studies, (3) the original search strategy was not readily available or could not be obtained from authors for replication, (4) risk factor was not addressed in an existing systematic review, or (5) existing reviews arrived at discordant conclusions.

As the aim of the National Population Health Study was to synthesize high quality, up-to-date evidence, conducting an update or de novo systematic review were proposed as the only two options. While it is recognized that conducting an update of a recent high quality review may be futile, the recency of systematic reviews was not a factor which was considered when developing the decision tool. In fact, there is currently “no formal consensus on when to update a systematic review”.⁵³ As such, all high quality reviews which adhered to the outlined criteria were eligible for an update irrespective of year of publication.

Using the decision tool, one updated review and one de novo systematic review were conducted. One high quality review reporting on the effect of Mediterranean diet adherence and risk of AD was identified and satisfied the eligibility criteria for an updated review. A de novo synthesis was conducted for a putative risk factor (i.e. psychological stress) which was not investigated in an existing review. The methodology and results of these reviews are reported in Chapters 4 and 5. While the remaining risk factors were also eligible for an update or de novo analysis, this was not feasible in the timeframe of the study.

Figure 1 – Decision tool for deciding on an updated review or de novo synthesis



2.3 Grading the Quality of Evidence

The quality of evidence was evaluated according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Evidence from observational studies are assigned a “low” grade.⁵⁴ However, certain conditions may warrant an increase in the overall grade of evidence. These criteria include the availability of strong or very strong evidence of an association with “no plausible confounders” or “no major threats to validity”, respectively.⁵⁴ Presence of a dose response relationship and evidence that “all plausible confounders would have reduced the effect” also necessitate an increase in the grade of evidence.⁵⁴ Results of this analysis were intended to justify the development of recommendations with respect to public health interventions.

CHAPTER 3: RESULTS AND DISCUSSION OF THE OVERVIEW OF REVIEWS

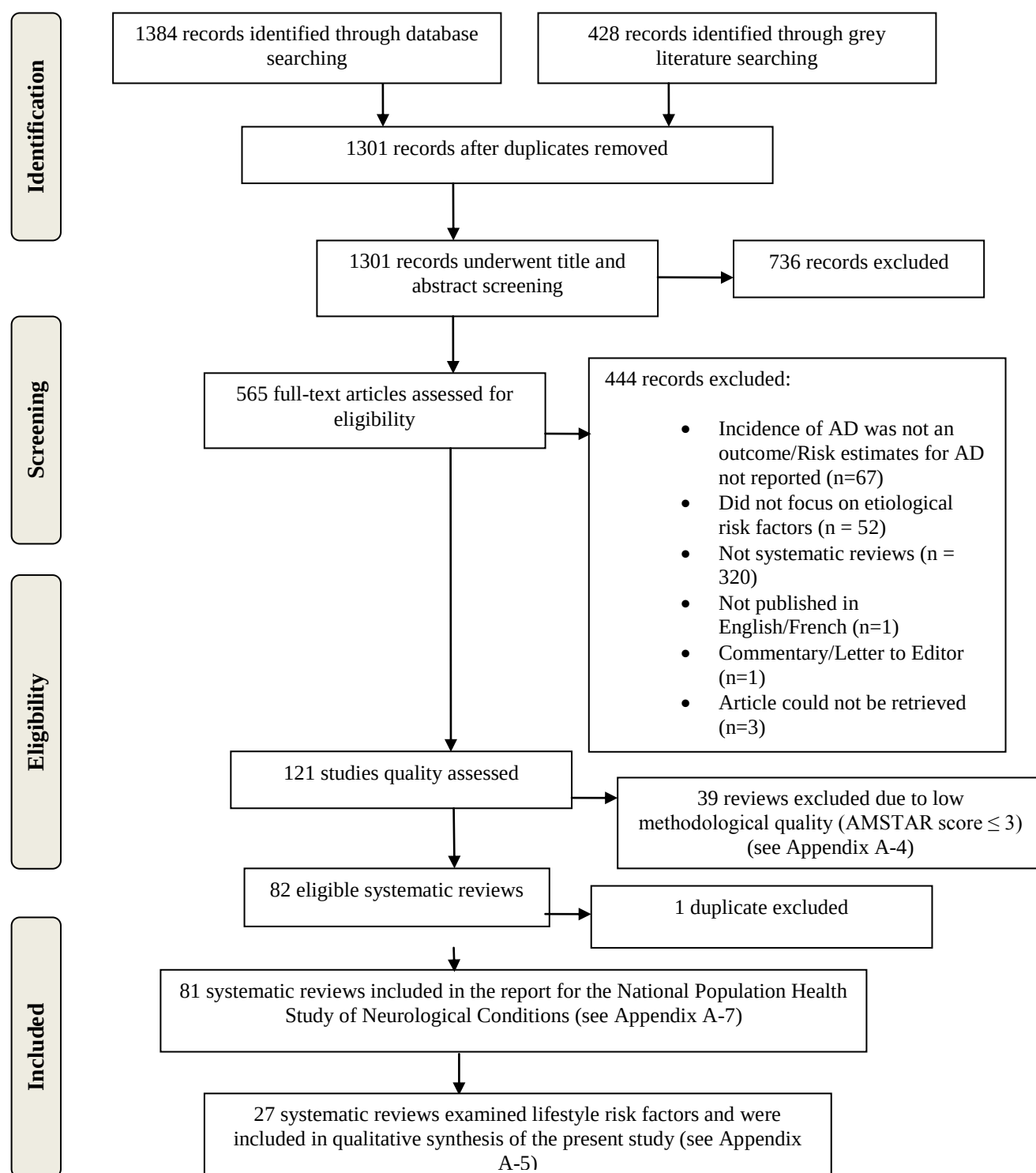
3.1 Literature Search Results

The database and grey literature search yielded 1384 and 428 records, respectively. A total of 1301 unique records remained after duplicates were removed in DistillerSR. The titles and abstract of the 1301 studies were reviewed according to the standard screening protocol. A total of 736 were excluded; the remaining 565 records underwent complete article screening. A total of 444 records satisfied one or more of the exclusion criteria and were consequently excluded. More specifically, 67 records were excluded because incidence of AD was not an outcome or the review did not adequately distinguish AD from all-cause dementia (i.e. risk estimates for AD were not reported), 52 records did not examine incidence of AD associated with exposure to a given etiological risk factor(s), 320 records did not adhere to our definition of a systematic review, one record was not published in English or French, one record was a commentary/letter to the editor, and three records were excluded because the entire publication could not be retrieved. Refer to Figure 2 for the flow of studies at each stage of the review process. A list of the 444 studies excluded in the secondary screening phase, along with reasons for exclusion, can be found in Appendix A-3.

A total of 121 relevant studies were quality assessed according to the AMSTAR instrument. Thirty-nine studies were deemed to be of low methodological quality (AMSTAR score ≤ 3) and were consequently excluded from the study. Refer to Appendix A-4 for a list of the excluded low quality systematic reviews accompanied by the assigned AMSTAR score. Refer to Appendix A-6 for details regarding the assessment of each AMSTAR item and the overall quality score assigned to each relevant study.

The remaining 82 studies were of moderate or high methodological quality. One⁵⁵ moderate quality review, identified through the OVID AutoAlerts feature, was excluded as it was a manuscript version of an identified Health Technology Assessment (HTA)²⁰. Consequently, the remaining 81 systematic reviews were included in the report for the National Population Health Study of Neurological Conditions. A list of the 81 reviews can be found in Appendix A-7. Of these 81 systematic reviews, 27 examined lifestyle risk factors and were included in the qualitative synthesis of the present study. The remaining reviews, which examined non-lifestyle risk factors, are reviewed separately and are not presented herein. Refer to Appendix A-5 for a list of reviews included in the present study.

Figure 2 - PRISMA Flow Diagram: Overview of Systematic Reviews



Template source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

3.2 Alcohol

Evidence from experimental and epidemiological studies suggest that light-to-moderate alcohol consumption may exert a protective effect against the development of AD and other cognitive outcomes.^{56,57} It has been suggested that the neuroprotection offered by alcoholic beverages is attributed to their antioxidant properties and pathways which mitigate the adverse effects of vascular risk factors for AD.^{20,56} Heavy alcohol consumption is presumed to be detrimental as it contributes to neurodegeneration.^{20,56}

The effect of alcohol consumption has been extensively reviewed. Ten systematic reviews were identified. Three reviews^{58,59,60} were later excluded due to low methodological quality. Seven moderate-quality systematic reviews^{20,56,57,61,62,63,64} were used to evaluate the association between alcohol consumption and risk of AD.

a) Study: Graves et al.⁶¹

Year: 1991

AMSTAR score: 4

The systematic review by Graves et al examined the effect of smoking and alcohol consumption on the risk of AD.⁶¹ Studies were identified through a search of the Medline database.⁶⁵ For the re-analysis conducted by Graves et al., original raw data from the eligible studies were used to derive risk estimates according to regression analysis.⁶⁵ The risk estimates were then synthesized quantitatively to yield a pooled estimate.⁶⁵ Presence of heterogeneity was addressed by sensitivity analysis in which outlying studies were omitted.^{61,65} Included studies were heterogeneous with respect to the type and quantity of alcohol under examination.⁶¹ According to the reviewers, this methodological heterogeneity necessitated the conversion of exposure data into a continuous variable representing ounces of pure alcohol intake per week.⁶¹ The data was then categorized into mild (<3.20 ounces/week), moderate (3.2-5.95 ounces/week), and heavy ($\geq$ 5.96 ounces/week) intake.⁶¹

Five case-control studies^{66,67,68,69,70} were eligible for inclusion in the pooled analysis. An aggregate of 814 cases and 840 controls were included. Exposure status for both cases and controls was ascertained according to data obtained from an informant in all five studies.⁶⁵

Results of the pooled analysis, adjusted for family history of dementia, suggest that when compared to abstinence, mild (RR: 0.97; 95% CI: 0.59, 1.60), moderate (RR: 0.75; 95% CI: 0.46, 1.20), and high (RR: 0.89; 95% CI: 0.52, 1.51) alcohol consumption was not significantly associated with risk of AD. A more rigorous attempt to control for potential confounders, namely head injury, education, and family history of dementia, yielded similar findings suggesting a lack of association between alcohol consumption and risk of AD (*Mild* – RR: 0.89; 95% CI: 0.59, 1.47. *Moderate* – RR: 0.82; 95% CI: 0.49, 1.39. *Heavy* – RR: 0.95; 95% CI: 0.51, 1.81). One⁶⁹ of the included studies categorized the exposure variable in a different manner as compared to the approach utilized by the remaining studies. As such, a sensitivity analysis excluding this study⁶⁹ was conducted. The sensitivity analysis also failed to reach statistical significance for all three categories of alcohol consumption (*Mild* – RR: 0.85; 95% CI: 0.48, 1.50. *Moderate* – RR: 1.48; 95% CI: 0.67, 3.23. *Heavy* – RR: 0.68; 95% CI: 0.31, 1.48).

Overall, results of the systematic review suggest that alcohol consumption was not significantly associated with risk of AD. Because the review relied on evidence from case-control studies, the results are limited by sources of bias inherent in studies which employ this methodological design. Case-control studies, in particular, are susceptible to recall bias.⁷¹ Case-control studies of cognitively impaired subjects face the added challenge of ascertaining exposure status of cognitively impaired or demented cases who often lack the capacity to recall past exposures.²¹ Consequently, a proxy respondent is often recruited to provide data for the purpose of exposure ascertainment.²¹ Recall bias may arise if the ability to recall past exposures is related to the outcome under investigation, resulting in “differential recall”.⁷² That is, if cases (or the proxy respondents of cases) are more likely to provide an accurate depiction of exposure history when compared to controls (or the proxy respondents of controls), or vice-versa, the derived risk estimate would be biased.⁷¹ The susceptibility for recall bias is further heightened if methods for exposure ascertainment are not parallel across outcome categories.⁷² Because an informant was used to ascertain exposure data for both cases and controls in all five studies, the likelihood of differential recall is minimized if we assume that the potential for recall error is similar for informants of cases as it is for informants of controls.⁷²

Secondly, the included case-control studies recruited both incident and prevalent cases of dementia which further increases the susceptibility to bias.⁶⁵ Reliance on prevalent cases increases the likelihood for recall error and makes it difficult to distinguish whether the exposure is associated with incidence or survival.⁷³ Results of the review should also be interpreted cautiously due to

methodological limitations at the review-level. Namely, the search of a single database and use of lenient inclusion criteria should be cited as important limitations of the review.

b) Study: Weih et al.⁶²

Year: 2007

AMSTAR score: 6

The systematic review by Weih et al. involved a search of Medline, Embase, Current Contents, and the Cochrane database.⁶² The search was supplemented by a review of a clinical trial register and of reference lists of pertinent papers.⁶² The review was restricted to longitudinal studies of disease-free populations.⁶² The Oxford Centre for Evidence-based Medicine criteria, which evaluates the strength of evidence for a given risk factor based on the methodological design of available studies, was used.⁶² A pooled analysis was not attempted.

Eight studies^{74,75,76,77,78,79,80,81} were eligible for inclusion. Three^{76,78,79} of the eight studies employed a nested case-control design which included an aggregate of 492 cases and 5893 controls. The remaining five cohort studies observed an aggregate of 490 cases (N = 10492) during periods of follow-up ranging from three to 23 years. Exposure status was ascertained according to self-report data collected through interview or completion of a questionnaire.⁶² AD was consistently diagnosed according to NINCDS-ADRDA and/or DSM (III-R, IV) criteria.⁶² There was heterogeneity across studies with respect to the type, amount, and categorization of alcohol consumption.⁶² Exposure status was defined as a dichotomous variable^{74,81} (e.g. drinkers vs. non-drinkers), according to categories delineated by quantity of consumption (e.g. “mild”, “moderate”, or specified quantity over a given time period) or broadly defined according to frequency of consumption (e.g. monthly, weekly).⁶² Finally, four studies^{75,76,78,80} stratified results according to type of alcoholic drink (i.e. wine, beer). Abstinence was used as reference category for all but one⁸¹ study. The remaining study reported risk estimates for non-drinkers.

Five studies^{75,76,78,79,80} reported a reduced risk of AD associated with alcohol consumption. One⁷⁹ nested case-control study reported a reduced odds of AD associated with mild (less than 1 drink per week) and moderate (1 to 6 drinks per week) alcohol consumption (*Mild* - RR: 0.60; 95% CI: 0.40, 0.90. *Moderate* - RR: 0.40; 95% CI: 0.30, 0.70). Four studies^{75,76,78,80} reported on the risk of AD associated with wine consumption. Despite obvious heterogeneity across studies with respect

to the quantity and frequency of consumption under examination, all four studies reported a statistically significant reduced risk of AD associated with wine consumption. More specifically, daily, weekly, and monthly consumption were associated with a reduced risk across studies (≥ 3 servings/day⁸⁰ - HR: 0.59; 95% CI: 0.38, 0.91; Weekly^{76,78} - OR: 0.49; 95% CI: 0.28, 0.88. RR: 0.33; 95% CI: 0.13, 0.86. Monthly⁷⁸ - RR: 0.43; 95% CI: 0.23, 0.82). One study⁷⁵ reported a marginally significant reduced odds of AD associated with mild and moderate wine consumption (*Mild* - OR: 0.55; 95% CI: 0.31, 0.99. *Moderate* - OR: 0.28; 95% CI: 0.08, 0.99). A single study reported on the association between beer consumption and risk of AD. The study⁷⁸ reported an increased risk of AD associated with monthly beer consumption (RR: 2.28; 95% CI: 1.13, 4.60).

Four studies^{74,76,77,81} failed to detect a statistically significant association between alcohol consumption, considered broadly, and AD (*Yoshitake et al.*⁷⁴ - RR: 0.56; 95% CI: 0.22, 1.43. *Ruitenbergh et al.*⁷⁷ - RR: 0.72; 95% CI: 0.43, 1.20. *Antilla et al.*⁸¹ - RR: 0.91; 95% CI: 0.39, 2.14. *Lindsay et al.*⁷⁶ - RR: 0.68; 95% CI: 0.47, 1.00).

Overall, the reviewers concluded that “most observational studies showed a dose-dependent effect on AD”.⁶² In particular, the reviewers noted that “moderate alcohol intake (several alcoholic drinks per week)” was associated with a reduced risk.⁶² Although the reviewers concluded that high consumption of alcohol was associated with an increased risk of AD according to “most studies”, risk estimates for heavy or excessive alcohol consumption were not reported in the review. The review is limited by the relatively small number of studies and the significant methodological heterogeneity with respect to the definition (i.e. type, quantity, and frequency) and categorization of the exposure variable.⁶²

c) Study: Patterson et al.⁶³

Year: 2007

AMSTAR score: 4

The systematic review conducted by Patterson et al. examined the effect of several putative risk factors on the development of AD and other cognitive outcomes including unspecified dementia and vascular dementia.⁶³ Studies were located using a search of Medline, Embase, and by reviewing the reference list of pertinent studies.⁶³ Studies excluded by the primary reviewer were verified by three

reviewers.⁶³ Duplicate, independent quality assessment and data extraction were carried out.⁶³ Longitudinal studies deemed to be methodologically sound were eligible for inclusion.⁶³ Methodological quality was ascertained according to the sampling strategy, exclusion of prevalent cases at baseline, completeness of follow-up, methods for exposure/outcome ascertainment, degree of confounding adjustment, and adequacy of the statistical analysis.⁶³

Two studies^{76,82}, one⁷⁶ of which was captured in the review reported by Weih et al.⁶², were eligible for inclusion. The cohort study⁸² included 2865 participants although the number of incident AD cases was not reported. The nested case-control study⁷⁶ included 194 cases and 3894 controls. The studies detected a reduced risk of AD associated with daily⁸² (250 to 500 ml/day-RR: 0.53; 95% CI: 0.30, 0.95) and weekly⁷⁶ (OR reported in section b) wine consumption. No conclusions, with respect to the effect of alcohol consumption, were drawn by reviewers.

d) Study: Peters et al.⁵⁶

Year: 2008

AMSTAR score: 6

The systematic review and meta-analysis by Peters' et al. examined the effect of alcohol consumption on the risk of incident AD and other cognitive outcomes.⁵⁶ A search of Medline, Embase, and PsychInfo was undertaken to locate studies published from 1995 to March 2006.⁵⁶ Inclusion of studies was restricted by methodological design with only longitudinal studies eligible for inclusion.⁵⁶ The screening and data abstraction process was duplicated and conducted independently by two reviewers.⁵⁶ The methodological quality of eligible studies was examined according to the criteria described by Kmet et al.⁸³ which evaluates several factors, namely, the study design, sampling strategy, and statistical analyses employed in a given study. Results were pooled according to the random effects model and statistical heterogeneity was examined according to the Cochran Q test and I^2 index.⁵⁶ The presence of publication bias was explored using funnel plots, the Begg-Mazumdar test, and Egger's regression test.⁵⁶

Eight longitudinal studies^{75,76,79,80,82,84,85,86}, which reported on risk of incident AD, were eligible for inclusion in the pooled analysis. Five of these studies^{75,76,79,80,82} were captured in earlier systematic reviews^{62,63}.

Four cohort studies reported the number of AD cases observed during follow-up. Among these studies, an aggregate of 398 cases (N = 5080) were observed during periods of follow-up ranging from three to 21 years. The number of AD cases was not reported in the remaining two cohort studies^{82,84}. Two nested case control studies^{76,79}, which included an aggregate of 452 cases and 4267 controls, were also included. A clinical diagnosis of AD was achieved according to the NINCDS-ADRDA criteria in a majority of studies.⁵⁶ All studies included in the meta-analysis provided risk estimates comparing drinkers to non-drinkers.⁵⁶ However, there was methodological heterogeneity across studies with respect to the quantity, type, and reporting of alcohol consumption. One study⁸⁴ reported on the effect of 3 to 4 glasses of alcohol a day, one study⁷⁶ reported on weekly consumption and provided risk estimates stratified by type of alcohol (i.e. wine, beer, spirits), two studies^{75,82}, reporting on the same cohort, examined the effect of varying quantities of wine consumption (*Orgogozo et al.*: ≤ 250 ml/day, 250-500 ml/day, ≥ 500 ml/day. *Larrieu et al.*: < 250 ml/day, 250-500 ml/day), two studies^{79,85} provided risk estimates for males and females separately with different thresholds of intake for each sex (*Huang et al.*: Males = 1-21 units/week; Females = 1-14 units/week. *Mukamal et al.*: Males = 1-6 drinks/week; Females = 7-13 drinks/week), one study⁸⁰ reported on the effect of 1 to 21 drinks of wine per week, and the quantity and type of alcohol under investigation was unclear in the remaining study⁸⁶.

Results of the random effects meta-analysis suggested that alcohol consumption was associated with a reduced risk of AD (RR: 0.57; 95% CI: 0.44, 0.74). However, there was evidence of heterogeneity across studies which is likely attributed to the heterogeneous definitions of exposure ($I^2 = 46\%$, Cochran Q = 22.23, df = 12, P = 0.035). There was no evidence of publication bias (Begg-Mazumdar test: Kendall's tau = -0.03, P = 0.86; Egger's test: 0.27; 95% CI: -2.16, 2.71, P = 0.81).⁵⁶

The reviewers concluded that these findings were suggestive of an association between alcohol consumption and a reduced risk of AD.⁵⁶ However, the review is limited by sources of methodological heterogeneity across studies with respect to the definition of the exposure (i.e. type, quantity), exposure ascertainment, and the degree of confounding adjustment.⁵⁶ Firstly, studies varied in terms of the beverage type (i.e. wine, spirits, beer) and quantity.⁵⁶ Of particular importance, the meta-analysis combined results pertaining to mild, moderate, and heavy alcohol consumption.⁵⁶ Secondly, there was heterogeneity across studies with respect to the timing of the exposure with some studies measuring past exposure while others restricted the analysis to current consumption.⁵⁶

e) Study: Anstey et al.⁵⁷

Year: 2009

AMSTAR score: 4

The systematic review by Anstey et al. attempted to collate the available evidence on the effect of alcohol consumption on risk of AD, all-cause dementia, vascular dementia and cognitive decline.⁵⁷ Studies were retrieved through a search of PubMed, PsychInfo, and the Cochrane Library with no restrictions on year of publication.⁵⁷ All studies published up to June 2007 were considered.⁵⁷ The search strategy was supplemented by handsearching of relevant studies.⁵⁷ Longitudinal studies which adequately excluded prevalent cases of dementia were eligible for inclusion.⁵⁷ Duplicate, independent screening of identified studies was conducted and data abstraction was performed by a single reviewer and verified by another.⁵⁷ The methodological quality of identified studies was not assessed. Heterogeneity across the included studies was examined using the chi-squared method.⁵⁷ In the presence of significant statistical heterogeneity, the random effects model was used to meta-analyze the data.⁵⁷ Otherwise, the fixed effects model was employed. The available data allowed for pooled estimates to be derived for current light/moderate consumption, heavy consumption, and alcohol consumption in general.⁵⁷ All categories were compared to abstinence.⁵⁷ Subgroup analysis by sex was conducted where data permitted.⁵⁷ The presence of publication bias was not examined.

A total of nine studies^{74,76,77,79,80,82,85,87,88} provided data on the risk of AD associated with alcohol consumption. All but two studies^{87,88} were captured in earlier systematic reviews^{56,62,63}. Six cohort studies reported the number of AD cases which amounted to an aggregate of 626 cases (N = 10721) observed during periods of follow-up ranging from two to seven years. The number of cases was unclear for one study⁸² which examined 2865 subjects. Two nested case control studies^{76,79}, which included an aggregate of 452 cases and 4267 controls, were also included. AD was consistently diagnosed according to NINCDS-ADRDA and/or DSM (III-R or IV) criteria. Studies varied with respect to the type (i.e. wine, beer, spirits), quantity, and categorization (i.e. non-drinkers vs. drinkers, light/moderate/heavy drinkers vs. non-drinkers) of the exposure.⁵⁷ A majority of studies examined current alcohol consumption.

Six studies^{77,79,80,82,85,87} reported on the effect of light-to-moderate alcohol consumption. All six studies reported risk estimates below 1.00, however, results reached statistical significance in only two studies^{79,87}. The pooled analysis detected a 28% reduced risk of AD associated with light-

to-moderate alcohol consumption (RR: 0.72; 95%CI: 0.61, 0.86). There was evidence of statistical heterogeneity which may be attributed to methodological diversity across studies with respect to the definition and measurement of the exposure ($\chi^2 = 11.43$, $p = 0.04$).⁵⁷ Light-to-moderate consumption was defined as one to 21 units of alcohol per week in two studies^{85,87} while one to 27 drinks per week⁸⁰, two to 28 drinks per week⁸², and one to 13 drinks per week⁷⁹ served as operational definitions in the remaining three studies. Compared to the range of consumption examined by Larrieu et al.⁸² (1-13 drinks), the threshold for moderate consumption was approximately doubled in the remaining studies. The reviewers also note that there was heterogeneity with respect to the quantity of alcohol constituting a “unit” or “drink”.⁵⁷

Three studies^{77,79,87} reported risk estimates stratified by sex allowing for subgroup analysis. According to the pooled analysis, light-to-moderate alcohol consumption was associated with a reduced risk of AD for both sexes, however, the association was more pronounced in males (*Males* – RR:0.58; CI 0.45, 0.75. *Females* –RR: 0.83; CI 0.81, 0.85). The observed difference may be attributed to the use of a uniform definition of exposure (“same number of drinks”) for both sexes in some of the included studies rather than a true biological difference attributed to sex.⁵⁷

Four studies^{77,79,87,88} evaluated the effect of heavy or excessive alcohol consumption. Results from all four studies failed to reach statistical significance. Heavy alcohol consumption was not significantly associated with risk of AD according to the pooled analysis (RR: 0.92; 95% CI 0.59, 1.45; Test for heterogeneity = Not statistically significant).

Two studies^{74,76} compared the risk of AD among drinkers compared to non-drinkers. Results of the pooled analysis suggested a reduced risk of AD associated with alcohol consumption (RR: 0.66; 95% CI: 0.47, 0.94). The analysis, however, is limited by the small number of studies suitable for inclusion.⁵⁷

The evidence summarized in the systematic review was suggestive of a reduced risk of AD associated with light-to-moderate late-life alcohol consumption.⁵⁷ Limitations of the systematic review warrant the cautious interpretation of the study findings.⁵⁷ Heterogeneity across studies with respect to the exposure definition (i.e. type, quantity, categorization), underrepresentation of heavy drinkers attributed to sources of selection bias, and the small number of studies reporting risk estimates stratified by sex, which precluded a robust subgroup analysis, were all noted as limitations.⁵⁷

f) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The HTA report by Williams et al. examined the effect of alcohol consumption on risk of AD.²⁰ Medline and the Cochrane Database of Systematic Reviews were searched to identify relevant systematic reviews.²⁰ Identification of a methodologically sound systematic review was supplemented by a search of the literature to identify primary studies published after the given review up to October 2009.²⁰ The quality of systematic reviews was examined according to criteria pertaining to the search strategy, eligibility criteria, quality assessment, statistical analyses, and the rigour to minimize bias.²⁰ Primary studies were quality assessed according to criteria put forth by the Agency for Healthcare Research and Quality (AHRQ), which takes into account the sampling strategy, methods for exposure/outcome ascertainment, degree of confounding adjustment, suitability of the statistical analyses, and thoroughness of reporting.²⁰

The report identified one systematic review⁵⁷ described in detail elsewhere (section e). According to findings of the identified review, the report concluded that light-to-moderate, but not heavy, alcohol consumption was associated with a reduced risk of AD.²⁰ The search for additional cohort studies did not yield results.²⁰

g) Study: Lee et al.⁶⁴

Year: 2010

AMSTAR score: 4

Lee et al. systematically reviewed the literature (PubMed, Embase, and PsychINFO) for longitudinal, community-cohort studies which examined the risk of dementia, cognitive impairment, and AD associated with alcohol consumption among elderly subjects (≥ 65 years).⁶⁴ Inclusion was restricted to studies of high methodological quality, which was established according to an assessment of the sampling strategy, methods for exposure/outcome ascertainment, degree of confounding adjustment, and completeness of follow-up.⁶⁴

Two cohort studies^{80,89}, in which an aggregate of 262 cases (N = 2569) were observed during periods of follow-up ranging from 4.1 to 6.3 years, were included. One⁸⁰ of the two studies was captured in earlier systematic reviews^{56,57,62}.

Alcohol consumption, defined as intake of sake one to two times per week, was not associated with AD risk according to one study⁸⁹ (RR: not reported). The remaining study⁸⁰ reported a reduced risk of AD associated with light (1 serving/month - 6 servings/week) to moderate (1-3 servings/day) wine consumption (HR: 0.55; 95% CI: 0.34, 0.89). The latter risk estimate is slightly different than that abstracted by Weih et al.⁶² as it was adjusted for all alcoholic beverages in addition to age, gender, education, and APOE allele.

As the reviewers also considered studies reporting on dementia and cognitive function, conclusions were not drawn specifically for AD. Taking all outcomes into consideration, the reviewers concluded that while light-to-moderate alcohol consumption was associated with a reduced risk of cognitive decline and dementia, heavy consumption was associated with a detrimental effect.⁶⁴ With respect to AD, a clear association, or lack thereof, between light-to-moderate consumption and risk of AD was not observed due to the small number of included studies. Moreover, neither of the two eligible studies reported on the effect of heavy consumption. Important methodological differences across the included studies must be considered. The studies examined different types of alcoholic beverages which may exert different effects depending on alcoholic content and varying properties. Moreover, the studies varied with respect to the quantities of beverage examined.

Discussion

Despite heterogeneity across systematic reviews with respect to the comprehensiveness of the employed search strategy, criteria to establish relevancy, and rigour to minimize bias, the identified reviews, for the most part, consistently detected a reduced risk of AD associated with alcohol consumption.

Reviews with primary study overlap rely on the same data and are consequently non-independent. In general, reviews with greater primary study overlap should arrive at concordant conclusions.⁹⁰ Despite sources of methodological heterogeneity, we would expect some degree of primary study overlap across reviews with similar research objectives. White et al.⁵¹ have

recommended the transparent reporting of the extent of primary study overlap. The recommended approach suggests the use of the most recent review as the referent.⁵¹ The number of overlapping studies between the referent and each previously published review was identified and presented in evidence tables throughout the chapter.⁵¹

The most recent reviews identified zero²⁰ and two⁶⁴ studies. As such, we used the review by Anstey et al.⁵⁷, which was published one year prior to the most recent reviews, as the referent. Because the HTA²⁰ relied on the referent review⁵⁷, the greatest degree of overlap was between these reviews. The lowest degree of primary study overlap (n=0) occurred between the referent review⁵⁷, which restricted inclusion to cohort studies, and that reported by Graves et al.⁶¹ Low overlap is explained by the unavailability of relevant cohort studies prior to 1995. As such, the review by Graves et al.⁶¹, which was published in 1991, relied solely on case-control studies. There was moderate overlap (n=5) between the referent review and reviews reported by Peters et al.⁵⁶ and Weih et al.⁶² Similarities across reviews with respect to the range of years searched and eligibility criteria serve as explanations for the degree of overlap.

Reviews attempting to collate evidence from several primary studies are often limited by sources of methodological heterogeneity across the included studies.^{20,56,57} Studies included in the identified reviews varied with respect to the definition and categorization of the exposure variable.^{20,56,57} Such variability limits comparability of studies, reduces the number of studies suitable for pooling, and may yield spurious results if studies are quantitatively synthesized.⁹¹

The observed association may be attributed to sources of bias. The study of lifestyle factors is affected by perceptions of health, which may impact the accuracy of the collected data.⁹² For example, healthy behaviours (e.g. dietary factors) may be overreported while unhealthy behaviours are underreported.⁹² Of particular importance, stigma associated with heavy alcohol consumption may serve as a barrier to accurate reporting of exposure history. Studies of behavioural factors are also limited by the aggregation of several lifestyle-related factors, which complicates the detection of the true effect of a given exposure.⁵⁷ Most studies included in the review by Anstey et al. attempted to tease out the effect of alcohol consumption by controlling for alcohol-related lifestyle factors which are also known to predispose to AD.⁵⁷ However, there was variability in the degree of confounding adjustment across primary studies and the possibility of residual confounding cannot be omitted.⁵⁶

Susceptibility to bias related to the inclusion of prevalent cases was addressed in the review by Anstey et al. which restricted the inclusion criteria to studies that adequately eliminated prevalent

cases at baseline.⁵⁷ Excluding such cases is imperative as exposure status may be altered as a result of diagnosis.⁹³

Limitations pertaining to case-control studies were described in the summary of the systematic review conducted by Graves et al.⁶¹ As addressed by Williams et al.²⁰, findings from the systematic review and meta-analysis reported by Anstey et al.⁵⁷ pertain to current alcohol consumption. Consequently, the effect of past exposure, which may vary from current consumption, is largely unknown.²⁰ The difference between former alcohol consumers and “lifetime abstainers” must also be considered.²⁰ As described by Williams et al., there is evidence to suggest that inclusion of former drinkers in the abstinence category may be problematic.²⁰ Findings suggesting an association between abstinence and an increased risk of cognitive impairment/AD may be attributed to the inclusion of former drinkers who may have ceased alcohol consumption as a result of morbidities associated with the outcome of interest.²⁰ Inclusion of former drinkers, who may be at higher risk for AD, in the abstinence category would give rise to misleading findings which suggest an increased risk of AD associated with non-drinking.²⁰ Finally, the effect of heavy alcohol consumption on AD and other cognitive outcomes is unclear. While some reviews concluded that excessive consumption was associated with an increased risk of AD, the only review⁵⁷ to quantitatively synthesize the available evidence found no association. As noted by the reviewers, the failure to detect an association may be attributed to sources of selection bias, namely, lower participation rates and greater attrition among heavy drinkers.⁵⁷ Moreover, heavy drinking is associated with higher mortality and morbidity. Consequently, heavy drinkers may not survive long enough to participate in research studies or may have co-morbidities that preclude recruitment.⁵⁷ The potential for selection bias must also be considered for other exposure categories as the association may differ among participants who enroll or remain in a study as compared to those who refuse participation or are lost to follow-up.^{94,95}

Considered cumulatively, the available evidence was suggestive of a reduced risk of AD associated with alcohol consumption. The most convincing evidence pertained to light-to-moderate quantities. Based on the limitations of the available literature, however, it is premature to provide recommendations pertaining to the alcoholic beverage or the quantity and frequency of consumption that may be associated with the greatest benefit.

Table 1 - Alcohol and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies^a	Results	Conclusion
Graves et al. ⁶¹ (1991)	Amstar score: 4 Publication Bias Assessed: No	To examine the effect of tobacco and alcohol consumption on the risk of AD.	All studies conducted before 1 January 1990	1. Medline	5	0 of 9	Mild (<3.20 ounces/week) vs. Non- drinkers: (RR: 0.97; 95% CI: 0.59, 1.60) Moderate (3.2-5.95 ounces/week) vs. Non- drinkers: (RR: 0.75; 95% CI: 0.46, 1.20) High (≥5.96 ounces/week) vs. Non- drinkers: (RR: 0.89; 95% CI: 0.52, 1.51)	Alcohol consumption was not associated with risk of AD.

Weih et al. ⁶² (2007)	Amstar Score: 6 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD.	January 1966 to June 2006	1. Medline 2. Embase 3. Cochrane Database 4. Current Contents	8	5 of 9	Three of eight studies failed to detect an association. Remaining five studies reported a significant or marginally significant protective effect of alcohol consumption (excluding beer) and AD. All studies (n=3) reporting on wine consumption detected a reduced risk of AD.	Moderate alcohol consumption exerts a protective affect while heavy consumption is detrimental.
Patterson et al. ⁶³ (2007)	Amstar Score: 4 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD and other cognitive outcomes.	1966 to December 2005	1. Medline 2. Embase	2	2 of 9	Two studies were eligible for inclusion. • Study 1: Moderate (250-500ml/day) wine consumption reduced risk of AD (RR: 0.53; 95% CI: 0.30, 0.95). • Study 2: Weekly wine consumption was protective (OR: 0.49; 95% CI: not reported).	No conclusions drawn by authors

Peters et al. ⁵⁶ (2008)	Amstar score: 6 Publication Bias Assessed: Yes, Funnel plots, Begg-Mazumdar test (Kendall's tau = -0.03, P = 0.86), Egger's test (0.27; 95% CI: -2.16, 2.71, P = 0.81), No indication of publication bias	To examine the effect of alcohol intake on the development of all-cause dementia, AD, and cognitive decline.	1995 to March 2006	1. Medline 2. Embase 3. PsychInfo	8	5 of 9	Drinkers vs. Nondrinkers (n=8): (RR: 0.57; 95% CI: 0.44, 0.74; Test for statistical heterogeneity: I^2 = 46%, Cochran Q = 22.23, df = 12, P = 0.035).	Evidence was suggestive of a reduced risk of AD associated with alcohol consumption
Anstey et al. ⁵⁷ (2009)	Amstar score: 4 Publication Bias Assessed: No	To examine the effect of alcohol intake on the development of all-cause dementia, AD, and cognitive decline.	All years from inception of the databases to June 2007	1. PubMed 2. PsychInfo 3. Cochrane Library	9	Referent	Light-to-moderate Drinkers vs. Nondrinkers (n=6): (RR: 0.72; 95% CI: 0.61, 0.86; Test for statistical heterogeneity: χ^2 = 11.43 p = 0.04). • Males (RR: 0.58; CI 0.45, 0.75). • Females (RR: 0.83; CI 0.81, 0.85). Heavy/excessive Drinkers vs.	Late-life alcohol consumption, particularly in light-to-moderate quantities, was protective against the development of AD.

							Nondrinkers (n=4): (RR: 0.92; 95% CI: 0.59, 1.45; Test for statistical heterogeneity = Not statistically significant) Drinkers vs. Nondrinkers (n=2): (RR: 0.66; 95% CI: 0.47, 0.94)	
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of alcohol	To examine the effect of several factors, including alcohol consumption, on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	0 *relied on referent review	0 of 9	Included the review by Anstey et al. which suggests that light-to-moderate alcohol consumption reduces risk of AD.	Light-to-moderate alcohol consumption was associated with a decreased risk of AD.
Lee et al. ⁶⁴ (2010)	Amstar Score: 4 Publication Bias Assessed: No	To examine the effect of several factors, including alcohol consumption, on the risk of developing AD and other cognitive impairments.	All years up to August 2008	1. Pubmed 2. Embase 3. PsychInfo	2	1 of 9	Two studies reported on risk of AD. - Study 1: No association between sake consumption (1-2 times/week) and risk of AD (RR: not reported). - Study 2: Light-to-moderate wine consumption	Light-to-moderate alcohol consumption reduces risk of cognitive decline and dementia. Association less clear for AD (too few studies). Heavy alcohol consumption increases risk of cognitive decline/dementia. No studies reported on risk of AD associated with heavy consumption.

							(HR: 0.55; 95% CI: 0.34, 0.89)	

^a“Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent”. Review by Anstey et al. selected as referent as the most recent reviews identified 0 to 2 studies. Item adopted from *White, CM et al.*⁵¹

3.3 Smoking

As a known risk factor for cardiovascular diseases that predispose to AD, smoking is a putative risk factor for the development of AD and other cognitive outcomes.^{97,99} Alternatively, there is evidence to suggest that nicotine, a compound found in tobacco, exerts a neuroprotective effect and ultimately improves cognitive functioning.⁹⁹

Twelve systematic reviews^{20,36,59,60,61,62,63,64,96,97,98,99} examined the association between smoking and risk of Alzheimer's disease. Three reviews^{36,59,60}, one³⁶ of which was an overview of reviews, received a low quality score according to the AMSTAR criteria and were excluded from further analysis. The remaining nine reviews were deemed to be of moderate methodological quality with AMSTAR scores ranging from 4 to 7.

a) Study: Graves et al.⁶¹

Year: 1991

AMSTAR score: 4

The systematic review by Graves et al.⁶¹ examined the effect of smoking and alcohol consumption on the risk of AD. Studies were identified through a search of the Medline database.⁶⁵ For the re-analysis conducted by Graves et al., original raw data from the eligible studies were used to derive risk estimates according to regression analysis.⁶⁵ The risk estimates were then synthesized quantitatively to yield a pooled risk estimate.⁶⁵ Presence of heterogeneity was addressed by sensitivity analysis in which outlying studies were omitted.^{61,65} Eight studies provided data for the analysis of ever (vs. never) smoking.⁶¹ To examine whether risk of AD varied with respect to the *quantity* of cigarettes smoked, data from six studies were used to derive pooled risk estimates for the effect of smoking less than one pack per day (<1 pack/day) and more than one pack per day (>1 pack/day).⁶¹ Four studies provided data allowing for analyses with respect to the effect of pack-year smoking history, which takes both intensity and duration of exposure into consideration.⁶¹ Pooled risk estimates were derived for three categories of pack-year smoking history: low (<15.5 pack-years), moderate (15.5 – 37.0), and high (>37.0).⁶¹ The analysis of pack-year smoking history was also stratified by family history of dementia.⁶¹ All exposure categories were compared to never smoking.⁶¹

Reviewers indicated that inclusion was restricted to studies which ascertained AD according to NINCDS-ADRDA, or DSM-III criteria.⁶⁵ Studies relying on criteria deemed to be “similar” to the NINCDS-ADRDA criteria (e.g. Blessed Dementia Scale⁶⁹) were also considered. To minimize the potential for recall bias, inclusion was restricted to studies which used similar methods for the exposure ascertainment of cases and controls.⁶⁵ More specifically, data obtained from a proxy informant was used to ascertain smoking status for all subjects.⁶⁵

The eight included studies^{66,67,69,70,100,101,102,103} examined an aggregate of 899 cases and 955 controls. When the derived risk estimates were pooled, ever smoking was associated with a reduced risk of AD (RR: 0.78; 95% CI: 0.62, 0.98). The test for heterogeneity was statistically significant. The sensitivity analysis excluding the outlying study¹⁰³ yielded a pooled risk estimate of 0.72 (95% CI: 0.56, 0.92). In the stratified analysis by family history of dementia, smokers with a positive and negative family history of dementia did not have a statistically significant reduced risk of AD (*Positive family history* – RR: 0.70; 95% CI: 0.48, 1.04. *Negative family history* – RR: 0.86; 95% CI: 0.63, 1.18). However, in the analysis excluding the outlying study¹⁰³, smoking was associated with AD in only those with a positive family history of dementia (*Positive family history* – RR: 0.63; 95% CI: 0.41, 0.94. *Negative family history* – RR: 0.81; 95% CI: 0.58, 1.13).

Six studies^{66,67,69,100,102,103} provided data on the risk of AD associated with the amount smoked per day. According to the pooled analysis, smoking less than one pack per day was associated with a reduced risk of AD while excessive smoking was not associated with AD (<1 pack/day – RR: 0.84 times; 95% CI: 0.75, 0.92; >1 pack/day - RR: 0.81; 95% CI: 0.53, 1.27). When the outlying study¹⁰³ (the only to report a risk estimate above 1.00) was excluded from the analysis, smoking less than one pack per day was no longer associated with a reduced risk of AD and excessive smoking was associated with a marginally significant reduced risk (<1 pack/day - RR: 0.80; 95% CI: 0.60, 1.07; >1 pack/day - RR: 0.66; 95% CI: 0.44, 1.00). Four studies^{66,69,100,102} provided data on the risk of AD associated with pack-year smoking history. Compared to never smokers, low pack-year smoking history (<15.5 pack-years) was not associated with AD (RR: 0.73; 95% CI: 0.50, 1.09). In contrast, moderate (15.5 – 37.0) and high (>37.0) pack-year smoking histories were associated with a reduced risk of AD (*Moderate* - RR: 0.63; 95% CI: 0.42, 0.95; *High* - RR: 0.50; 95% CI: 0.31, 0.80). The trend was statistically significant (p = 0.0003) suggesting that risk of AD decreased with increasing pack-year history.⁶¹ Among those with a positive family history, low and moderate pack-year smoking history were not associated with a reduced risk (*Low* - RR: 0.53; 95% CI: 0.26, 1.10. *Moderate*– RR: 0.49; 95% CI: 0.24, 1.02). However, among this

group, a high pack-year smoking history was associated with a reduced risk of AD (RR: 0.37; 95% CI: 0.17, 0.81). The trend was not statistically significant, however (p=0.11). Among those with a negative family history of dementia, low, moderate, and high pack-year histories were not associated with AD risk (*Low* - RR: 0.85; 95% CI: 0.52, 1.38. *Moderate*– RR: 0.69; 95% CI: 0.39, 1.22. *High* – RR: 0.66; 95% CI: 0.33, 1.34). The p-value for the trend test was not statistically significant (p=0.11). Finally, smoking was significantly associated with AD among late-onset cases (*Early onset* – RR: 0.89; 95% CI: 0.67, 1.19. *Late-onset* – RR: 0.65; 95% CI: 0.43, 0.96).⁶¹

Based on an analysis of eight case-control studies, the reviewers concluded that smoking was associated with a statistically significant reduced risk of AD.⁶¹ The reviewers cautioned that prospective cohort studies were required to confirm the association.⁶¹

b) Study: Almeida et al.⁹⁶

Year: 2002

AMSTAR score: 4

The systematic review and meta-analysis conducted by Almeida et al. examined the effect of “ever smoking” and risk of AD.⁹⁶ Relevant studies were identified through a search of Medline, PsycINFO, and via handsearching. The methodological quality of relevant studies was examined according to several criteria, namely, sampling strategy, methods for exposure/outcome ascertainment, appropriateness of statistical analyses, completeness of follow-up, and adequacy of confounding adjustment.⁹⁶ The presence of statistical heterogeneity across the included studies was examined and fixed effects meta-analyses were conducted to obtain pooled risk estimates. Separate pooled risk estimates were obtained for case-control and cohort studies and subgroup analyses according to study quality were conducted.

A total of 21 case-control^{67,69,70,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117} and eight cohort^{117,118,119,120,121,122,123,124} studies were eligible for inclusion in the review. The case-control studies included an aggregate of 2212 cases and 3111 controls. One included study¹²² was a pooled analysis of four population-based cohort studies which included an aggregate of 16334 participants of which 277 subjects with incident AD provided data regarding smoking. The pooled analysis study¹²² included subjects from one cohort study¹²⁴ also included in the review. The study¹²⁴

examined 6870 subjects, 105 of which developed AD over two years of follow-up. The remaining cohort six cohort studies observed an aggregate of 774 cases of AD (N = 291461) over periods of follow-up ranging from two to 27 years.

Among the included studies, a positive diagnosis of AD was obtained according to NINCDS-ADRDA (n=17), ICD-10 (n=1), and DSM-III-R (n=3) criteria.⁹⁶ In four studies, AD was diagnosed according to death certificates¹¹⁸, the Blessed Dementia Scale⁶⁹ and according to alternate criteria^{102,104}. Methods employed for the diagnosis of AD were unclear in four studies^{67,108,109,120}. Studies were heterogeneous with respect to the exposure definition.⁹⁶ Thirteen case-control and all of the identified cohort studies examined the effect of “ever” smoking.⁹⁶ The definition of “smoking” was marked as “unclear” by reviewers for five case-control studies^{70,102,108,109,113}. One case-control study¹¹¹ solely reported on the effect of current smoking, one¹¹⁰ examined the effect of a minimum threshold of exposure (≥ 20 pack-year lifetime history), and one¹¹⁶ reported on the effect of categories of exposure (i.e. light, daily) without specifying the timing of exposure (i.e. past or present).⁹⁶ For case-control studies, exposure status was ascertained according to self-report data obtained from the participant or from a proxy respondent, which in most cases was a family member (next of kin) or caregiver.⁹⁶

Results from the fixed effects meta-analysis including all 21 case-control studies (n=5323), irrespective of study quality, suggested that “ever having smoked” was associated with a statistically significant decreased odds of AD (OR: 0.74; 95% CI: 0.66, 0.84; Test for heterogeneity: p = 0.246). The subgroup analysis restricted to the eight higher quality ($\geq 26/52$) case-control studies^{69,70,100,101,105,114,115,117} suggests that smoking was associated with a decreased odds of AD (OR: 0.82; 95% CI: 0.70, 0.97; Test for heterogeneity: p = 0.279). Two studies^{107,113}, which scored 26 points or higher, were excluded from the analysis without explanation. In a subsequent analysis restricted to higher quality ($\geq 26/52$) case-control studies^{69,70,101,107} which controlled for confounding by matching cases and controls, the risk estimate failed to reach statistical significance (OR: 0.82; 95% CI: 0.53, 1.27; Test for heterogeneity: p = 0.283).

A meta-analysis combining results from six cohort studies was conducted. One study¹²⁴ was excluded from the analysis in an effort to avoid double counting subjects (i.e. the same subjects were included in a study¹²² reporting a pooled analysis of four population-based cohort studies). A second study¹²⁰, which did not adequately report the “exact number of cases at risk that were followed-up until death” was also excluded.⁹⁶ The pooled analysis, which included 43885 participants, yielded a risk estimate exceeding 1.00. However, results failed to reach statistical significance (RR: 1.10; 95%

CI: 0.94, 1.29). The test for heterogeneity was significant ($p = 0.004$). The subgroup analysis restricted to methodologically rigorous cohort studies^{116,118,122,123} ($\geq 13/26$) also failed to detect an association (RR: 1.12; 95% CI: 0.93, 1.34; Test for heterogeneity: $p = 0.308$). Lastly, a sensitivity analysis restricted to cohort studies^{122,123} that reported “the number of subjects who were smokers at baseline and later developed AD” detected a two-fold increased risk of AD associated with smoking (OR: 1.99; 95% CI: 1.33, 2.98).⁹⁶ However, results of the analysis were limited by the small number of eligible studies ($n=2$).⁹⁶

Results from the overall pooled analysis of case-control studies suggested that history of smoking was associated with a reduced risk of AD.⁹⁶ However, the series of sensitivity analyses combining results of the most methodologically rigorous case-control studies failed to detect an association suggesting that the observed association may have been due to sources of bias.⁹⁶ Furthermore, analyses restricted to cohort studies yielded risk estimates exceeding 1.00.⁹⁶ Although cohort studies are generally less susceptible to bias, the analysis of cohort studies was based on findings from a limited number of heterogeneous studies. Due to these inconsistent findings, the reviewers concluded that the association between smoking and risk of AD was “unclear”.⁹⁶

c) Study: Anstey et al.⁹⁷

Year: 2007

AMSTAR score: 4

The systematic review and meta-analysis by Anstey et al. examined the association between smoking and risk of AD and other cognitive outcomes.⁹⁷ Studies were identified through a search of PubMed, PsychINFO, and Cochrane CENTRAL unrestricted by year of publication.⁹⁷ The search was also supplemented by handsearching the citations of pertinent articles.⁹⁷ Inclusion was restricted to longitudinal studies that excluded prevalent cases at baseline and had an adequate length of follow-up (≥ 1 year).⁹⁷ Data extraction was carried out by one reviewer and verified by another.⁹⁷ Methodological quality of identified studies was not evaluated.⁹⁷

As reported by the reviewers, ten studies, representing 13786 participants, provided data pertaining to association between smoking and AD.⁹⁷ Two^{123,129} of the ten included publications reported on the same cohort of subjects. One¹²³ reported 246 incident cases of AD ($N = 1138$) observed over 5.5 years of follow-up. The other¹²⁹ reported 142 cases of AD ($N = 1204$) observed

over two years of follow-up. The remaining studies examined 850 cases of AD and had periods of follow-up ranging from two to 30.3 years. All 10 studies employed acceptable criteria for the diagnosis of AD with nine studies using the NINCDS-ADRDA criteria and one study using the modified DSM-III-R criteria.⁹⁷ Smoking status was ascertained through self-reported data at baseline and was re-evaluated at follow-up.⁹⁷ Five studies^{122,123,125,126,127} reported on current and former smoking, three studies^{76,117,128} solely reported on the effect on ever smoking, and the remaining two studies^{74,129} solely reported risk estimates for current smoking. Heterogeneity across the included studies was examined using the χ^2 method.⁹⁷ In the presence of significant statistical heterogeneity, the random effects model was used to meta-analyze the data.⁹⁷ Otherwise, the fixed effects model was employed.⁹⁷

Current smoking was associated with an increased risk of AD when compared to never (n=4) and former (n=4) smoking (*Never* - RR: 1.79; 95% CI: 1.43, 2.23; Test for heterogeneity: p = 0.50. *Former* - RR: 1.70; 95% CI: 1.25, 2.31; Test for heterogeneity: p = 0.60). The pooled risk estimate did not reach statistical significance when current smoking was compared to the combined category of past and never smoking (RR: 1.25; 95% CI: 0.49, 3.17; Test for heterogeneity: p = 0.03). The analysis was limited by the small number of studies (n=2) reporting on this association as well as obvious heterogeneity.⁹⁷ Compared to never smoking, ever (n=3) and former (n=5) smoking was not associated with AD (*Ever* - RR: 1.21; 95% CI: 0.66, 2.22; Test for heterogeneity: p = 0.01. *Former* - RR: 1.01; 95% CI: 0.83, 1.23; Test for heterogeneity: p = 0.26).

Results of the review were suggestive of an increased risk of AD associated with current smoking.⁹⁷ However, self-reported former and ever smoking showed no association with AD.⁹⁷ According to the reviewers, the former and ever smoking exposure categories were poorly defined and may include a group of people with diverse smoking histories with respect to quantity and duration of exposure.⁹⁷ These heterogeneous exposure categories serve as a limitation of the review and may offer an explanation for the null findings for these exposure groups.⁹⁷ Furthermore, the limited number of available studies, presence of statistical heterogeneity, and variation in the degree of confounding adjustment between studies also serve as important limitations of the review.⁹⁷

d) Study: Patterson et al.⁶³

Year: 2007

AMSTAR score: 4

The systematic review conducted by Patterson et al. examined the effect of several putative risk factors on the development of AD and other cognitive outcomes including unspecified dementia and vascular dementia.⁶³ Studies were located using a search of Medline, Embase, and by reviewing the reference list of pertinent studies.⁶³ Studies excluded by the primary reviewer were verified by three reviewers.⁶³ Duplicate, independent quality assessment and data extraction were carried out.⁶³ Longitudinal studies deemed to be of “fair” or “good” quality were eligible for inclusion.⁶³ Methodological quality was ascertained according to several criteria pertaining to the sampling strategy, exclusion of prevalent cases at baseline, completeness of follow-up, methods for exposure/outcome ascertainment, degree of confounding adjustment, and adequacy of the statistical analysis.⁶³

The reviewers identified the systematic review reported by Almeida et al.⁹⁶. According to the analysis restricted to methodologically sound prospective cohort studies, the included review reported a two-fold increased risk of AD associated with smoking (OR: 1.99; 95% CI: 1.33, 2.98).⁶³

e) Study: Weih et al.⁶²

Year: 2007

AMSTAR score: 6

The systematic review by Weih et al. involved a search of Medline, Embase, Current Contents, and the Cochrane database.⁶² The search was supplemented by a review of www.clinicaltrialresults.org and of reference lists of pertinent papers. The review was restricted to longitudinal studies of disease-free populations.⁶² The Oxford Centre for Evidence-based Medicine criteria, which evaluates the strength of evidence for a given risk factor based on the methodological design of available studies, was used.⁶² A pooled analysis was not attempted.

Five studies^{74,76,122,123,124} were included. One included study¹²² was a pooled analysis of four population-based cohort studies (N = 16334). The pooled analysis study¹²² included subjects from one of the cohort studies¹²⁴ included in the review. The study¹²⁴ examined 6870 subjects, 105 of which developed AD over two years of follow-up. The remaining cohort studies included an aggregate of 378 cases of AD (N = 6005) and had periods of follow-up ranging from two to seven years. A clinical diagnosis of AD was consistently achieved according to the NINCDS-ADRDA or

DSM (III-R or IV) criteria. Smoking status was ascertained according to self-reported data collected via interview or questionnaire.⁶² Follow-up duration ranged from two to seven years. All three studies reporting on the association between current (versus never) smoking and AD identified an increased risk (*Ott et al.*¹²⁴ – RR: 2.30; 95% CI: 1.30, 4.10. *Launer et al.*¹²² – RR: 1.74; 95% CI: 1.21, 2.50. *Merchant et al.*¹²³ – RR: 1.70; 95% CI: 1.10, 2.80). One study failed to detect an association between current smoking and AD. However, unlike the other studies reporting on current smoking, this study used former and never smokers as the comparator (*Yoshitake et al.*⁷⁴ – RR: 0.73; 95% CI: 0.34, 1.57). The remaining study reported no association between ever (versus never) smoking and AD (*Lindsay et al.*⁷⁶ – RR: 0.82; 95% CI: 0.57, 1.17). The reviewers concluded that the evidence was suggestive of an increased risk of AD associated with smoking.⁶²

f) Study: Peters et al.⁹⁹

Year: 2008

AMSTAR score: 6

The effect of current and former smoking on the risk of AD and other cognitive outcomes were reviewed by Peters et al.⁹⁹ Relevant studies published between 1996 and 2007 were identified through a database search (Medline, Embase, PsychINFO, Cochrane Database).⁹⁹ Case-control and cohort studies were considered. Duplicate, independent screening of studies was conducted to minimize bias. Disagreements were resolved by consensus.⁹⁹

Eleven studies^{76,117,118,122,123,124,126,129,130,131,132} reporting on the association between smoking and risk of AD were identified. Two publications^{124,132} reported on the Rotterdam cohort and another two^{123,129} on the WHICAP cohort. Of those reporting on the WHICAP cohort, one¹²³ reported 246 incident cases of AD (N = 1138) observed over 5.5 years of follow-up and the other¹²⁹ reported 142 cases of AD (N = 1204) observed over two years of follow-up. Of those reporting on the Rotterdam cohort, one¹³² reported 555 cases of AD (N = 6868) observed over 7.3 years of follow-up whereas the other¹²⁴ reported 105 cases of AD (N = 6870) observed over two years of follow-up. Another included study¹²², which reported a pooled analysis of four population-based cohort studies, also included members of the Rotterdam cohort. The remaining studies observed 965 cases of AD (N = 35565) over periods of follow-up ranging from two to 25 years of follow-up. A positive diagnosis of AD was reached according to NINCDS-ADRDA and DSM-III criteria in a majority of the studies.

Exposure ascertainment was based on self-reported data in all studies.⁹⁹ Statistical heterogeneity was examined according to the Cochran Q test and random effects meta-analyses were conducted to examine the effect of former and current smoking on the risk of AD.⁹⁹ The extent of publication bias was examined through visual inspection of funnel plot asymmetry.⁹⁹

Seven of the ten studies, which examined the association between current smoking and AD, reported a statistically significant increased risk. According to the random effects meta-analysis (n=8), current smoking was associated with an increased risk of AD (RR: 1.59; 95% CI: 1.15, 2.20). There was evidence of statistical heterogeneity suggesting that the included studies were clinically or methodologically heterogeneous (Cochran Q = 23.25, p= 0.0015). Visual inspection of the funnel plot suggests the absence of publication bias for the analysis of current smoking.⁹⁹

All eight studies which examined the effect of former smoking on AD risk failed to detect an association. While four studies reported risk estimates exceeding 1.00, the remaining four reported a nonsignificant decreased risk of AD among former smokers. These conflicting results may be attributed to the heterogeneous definition of “former smoking” across the included studies.^{97,99} In the random effects meta-analysis, former smokers were not at an increased risk of developing AD when compared to non-smokers (RR: 0.99; 95% CI: 0.81, 1.23). The test for heterogeneity was not statistically significant (Cochran Q = 11.27, p = 0.08). The funnel plot was symmetrical suggesting the absence of publication bias for the analysis of former smoking.⁹⁹

Overall, the reviewers concluded that there was evidence to suggest that current smoking was associated with an increased risk of AD. Failure to detect an association between AD and former smoking was possibly attributed to the lack of a standardized definition for the former smoking category.^{97,99} Consequently, studies were likely heterogeneous with respect to the smoking history of former smokers, namely pertaining to smoking duration and cessation time.⁹⁹ Heterogeneity across the included studies with respect to length of follow-up, population characteristics, country of origin, and sample size were also cited as important limitations of the review.⁹⁹ Sources of methodological and clinical heterogeneity may explain the statistical heterogeneity observed in the meta-analysis examining the effect of current smoking. The limited number of available studies may have precluded sensitivity analyses that would confirm the source of the observed statistical heterogeneity.

g) Study: Cataldo et al.⁹⁸

Year: 2010

AMSTAR score: 7

The systematic review and meta-analysis by Cataldo et al. examined the risk of Alzheimer's disease associated with cigarette smoking.⁹⁸ The reviewers adjusted for industry affiliation, a factor known to influence study findings, introduce bias, and lead to spurious results.⁹⁸ Studies were retrieved through a search of PubMed, PsychINFO, and Cochrane CENTRAL.⁹⁸ Relevant studies were handsearched for additional studies and a search of the grey literature was conducted using Google Scholar.⁹⁸ Industry affiliation was ascertained according to data retrieved from the Legacy Tobacco Documents Library.⁹⁸ The screening and/or extraction phase was partially duplicated.⁹⁸

A total of 43 studies (26 case-control and 17 cohort studies), reported in 40 publications, satisfied the inclusion criteria of the review. The case-control studies included an aggregate of 4674 cases and 3838 controls. One included study¹²² was a pooled analysis of four population-based cohort studies (N = 16334). Two publications reported on the WHICAP cohort. One¹²³ reported 246 incident cases of AD (N = 1138) observed over 5.5 years of follow-up and the other¹²⁹ reported 142 cases of AD (N = 1204) observed over two years of follow-up. The remaining studies observed an aggregate of 1905 cases with information on smoking (N = 309711) over periods of follow-up ranging from two to 30 years. Of the 26 case-control studies, 18 studies were not affiliated with tobacco industries.⁹⁸ Fourteen of the 17 included cohort studies were unaffiliated. AD was diagnosed according to NINCDS-ADRDA (n=18), ICD-10 (n=1), DSM-III-R/DSM-IV (n=2), Blessed Dementia Scale (n=2), NIH criteria (n=1), and alternate criteria (n=1).⁹⁸ The method used for AD diagnosis was unclear in one case-control study. Among the cohort studies, 12 used the NINCDS-ADRDA criteria, one relied solely on used the DSM-III-R criteria, three studies used both NINCDS-ADRDA and DSM-III/DSM-IV criteria, and the final study used MMSE and DSM-III-R criteria for outcome ascertainment.⁹⁸ While "ever versus never" smoking was investigated in a majority of the included studies, smoking was categorized as former/past or current smoking in some studies.⁹⁸ Methods employed for exposure ascertainment across the included studies was not clearly specified in the review. The presence of heterogeneity across the included studies was examined using the Q-statistic and random effects meta-analyses were conducted to obtain pooled risk estimates.⁹⁸ Separate pooled risk estimates were reported for case-control and cohort studies and subgroup analyses stratified by tobacco-industry affiliation were conducted.⁹⁸ Publication bias was

explored using Begg's funnel plot.⁹⁸ The influence of study design, quality, and industry affiliation was examined using regression analysis.⁹⁸

The pooled analysis of industry affiliated cohort studies yielded nonsignificant findings (RR: 0.60; 95 % CI: 0.27, 1.32). Industry affiliated case-control studies detected a reduced risk of AD associated with cigarette smoke (OR: 0.86; 95 % CI: 0.75, 0.98). The pooled analysis of unaffiliated case-control failed to reach statistical significance (OR: 0.91; 95% CI: 0.75, 1.10). Alternatively, when unaffiliated cohort studies were quantitatively synthesized, smoking was associated with an increased risk of AD (RR: 1.45; 95% CI: 1.16, 1.80). The only cohort study¹²¹ to detect a protective association was industry affiliated. The remaining affiliated cohort studies^{117,119} did not detect an association. Among the 14 unaffiliated cohort studies, six^{120,123,126,128,129,131} detected an increased risk of AD among smokers. As noted by the reviewers, there was evidence of statistical heterogeneity in the pooled analyses of cohort studies.

In addition to reviewing original studies, the reviewers also examined existing systematic reviews. A total of 10 systematic reviews were evaluated, four of which were affiliated with the tobacco industry.⁹⁸ Out of the 10 systematic reviews, only the four affiliated reviews concluded that smoking was associated with a reduced risk. Statistical tests confirmed that results of the reviews were influenced by industry affiliation ($P = 0.005$). Finally, results from Begg's funnel plot suggested the absence of publication bias.⁹⁸

The pooled analysis of industry affiliated cohort studies and that of case-control studies, irrespective of industry affiliation, yielded risk estimates below 1.00. Industry affiliated studies are susceptible to bias as a result of industry influence.⁹⁸ For example, industry affiliated studies are "more likely to...experience publication bias, publication delays and data withholding".⁹⁸ The analysis restricted to unaffiliated cohort studies was suggestive of an increased risk of AD associated with smoking.⁹⁸ Results of the multiple regression analysis confirmed that industry affiliation influenced study findings ($P = 0.008$).⁹⁸ Furthermore, results derived from case-control studies differed from those derived from cohort studies ($P = 0.075$).⁹⁸ More specifically, case-control and industry affiliated studies were more likely to produce results suggestive of a protective association.⁹⁸ Overall, the reviewers concluded that smoking appeared to increase the risk of AD.⁹⁸

h) Study: Lee et al.⁶⁴

Year: 2010

AMSTAR score: 4

Lee et al. systematically reviewed the literature for longitudinal, cohort studies which examined the risk of AD associated with smoking among elderly subjects (≥ 65 years).⁶⁴ Inclusion was restricted to studies of high methodological quality, which was established according to an assessment of several criteria, namely, sampling strategy, methods for exposure/outcome ascertainment, degree of confounding adjustment, and completeness of follow-up.⁶⁴

Four studies, which examined the effect of smoking on the development of AD, were identified. Two^{124,132} of the four studies examined the same cohort of subjects. One¹³² examined 6868 subjects, 555 of which developed AD over seven years of follow-up. The second¹²⁴ examined 6870 subjects, 105 of which developed AD over two years of follow-up. The remaining studies observed an aggregate of 161 cases of AD (N = 4681) over periods of follow-up ranging from 21 to 25 years. Two publications reporting on the same cohort^{124,132} reported risk estimates for current vs. never smokers. Both reported an increased risk associated with current but not former smoking (Current: *Reitz et al.*¹³² - HR: 1.51; 95% CI: 1.10, 2.08. *Ott et al.*¹²⁴ - RR: 2.30; 95% CI: 1.30, 4.10. Former: RRs not reported in the review). One¹³² also reported an increased risk associated with a greater than 20 pack-year smoking history (HR: 1.82; 95% CI: 1.26, 2.57). Heavy smoking was associated with an increased risk of AD according to another study¹³⁰ (OR: 2.93; 95% CI: 1.37, 6.53). The final study¹³³ reported that ever smoking was associated with an increased risk of AD among carriers of the APOE e4 allele (RR: not reported). The reviewers concluded that smoking was associated with an increased risk of AD according to the identified evidence.⁶⁴

i) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The HTA report by Williams et al. examined the effect of smoking on risk of AD.²⁰ Medline and the Cochrane Database of Systematic Reviews were searched to identify relevant systematic

reviews. Identification of a methodologically sound systematic review was supplemented by a search of the literature to identify primary studies published after the given review up to October 2009.²⁰ The quality of systematic reviews was examined according to criteria pertaining to the search strategy, eligibility criteria, quality assessment, statistical analyses, and the rigour to minimize bias.²⁰ Primary studies were quality assessed according to criteria put forth by the Agency for Healthcare Research and Quality (AHRQ), which takes into account the sampling strategy, methods for exposure/outcome ascertainment, degree of confounding adjustment, suitability of the statistical analyses, and thoroughness of reporting.²⁰

The report identified two relevant systematic reviews.^{97,99} However, only findings reported by Anstey et al.⁹⁷ were presented as it was deemed to be more comprehensive and transparently reported.²⁰ According to the results of the identified review, current but not former smoking was associated with an increased risk of AD. Findings of the identified review are discussed in detail elsewhere (section c).

Two recent cohort studies^{131,132} were also identified and included in the report. One study¹³¹ examined 1064 subjects, 170 of which developed AD over 4.1 years of follow-up. The other¹³² reported 555 cases of AD (N = 6868) over 7.3 years of follow-up. Both studies reported risk estimates for current and former smoking and also presented results stratified by APOE e4 status.²⁰ Both studies detected an increased risk of AD associated with current but not former smoking current (Current: *Aggarwal et al.*¹³¹ – OR: 3.40; 95% CI: 1.44, 8.01. *Reitz et al.*¹³² – RR: 1.51; 95% CI: 1.10, 2.08; Former: *Aggarwal et al.*¹³¹ – OR: 0.90; 95% CI: 0.47, 1.70. *Reitz et al.*¹³² – RR: 1.17; 95% CI: 0.90, 1.52). The association between current smoking and risk of AD was modified by APOE e4 status.²⁰ Both studies reported an increased risk of AD associated with current smoking among APOE e4 non-carriers but not among carriers (Non-carriers - *Aggarwal et al.*¹³¹ – OR: 4.32; 95% CI: 1.28, 14.65. *Reitz et al.*¹³² – RR: 1.95; 95% CI: 1.29, 2.95. Carriers - *Aggarwal et al.*¹³¹ – OR: 0.57; 95% CI: 0.11, 3.12. *Reitz et al.*¹³² – RR: 1.06; 95% CI: 0.62, 1.79).²⁰ The interaction between APOE e4 status and former smoking was less clear.²⁰ Based on the available literature, the reviewers concluded that the evidence was suggestive of an increased risk of AD associated with current smoking.

Discussion

Discordance across reviews

Of the nine identified systematic reviews reporting on smoking, one⁶¹ concluded that smoking was associated with a reduced risk of AD, one⁹⁶ reported that the association was unclear, and the remaining seven concluded that smoking appeared to increase risk of AD. Synthesizing the results of the identified systematic reviews is challenged by these discordant conclusions. According to Jadad et al.⁹⁰, discordance arises as a result of methodological differences across reviews. Methodological heterogeneity with respect to the “clinical question, study selection and inclusion, data extraction, assessment of study quality, assessment of the ability to combine studies, and statistical methods for data analysis” were all described as potential explanations of discordance.⁹⁰ The conclusions of a systematic review are dependent on the identified and included evidence.⁹⁰ Study identification and inclusion is directly linked to the study objective or clinical question, the search strategy, and the employed eligibility criteria. The following section will outline examples of methodological differences across reviews relating to these factors.

Reviews reporting on smoking differed with respect to their objectives. Six^{20,61,96,97,98,99} of the nine reviews specifically sought primary studies which reported on the effect of smoking (i.e. smoking-specific reviews). In comparison to reviews that reported on multiple putative risk factors^{62,63,64}, smoking-specific reviews yielded more smoking-related primary studies. Systematic reviews that reported on numerous risk factors yielded one⁶³ to five⁶² primary studies. In contrast, smoking-specific reviews (with the exception of Williams et al.²⁰ which yielded a small number of studies due to narrow publication year limits) identified eight⁶¹ to forty-three⁹⁸ studies. As the objective of a given review is likely to drive the search strategy, reviews with heterogeneous objectives are expected to vary with respect to the yield of identified studies. Reviews specifically interested in the effect of smoking were more likely to employ smoking-related keyword and MeSH search terms (i.e. “smoking”, “tobacco”, “cigarettes”, and “nicotine”) as opposed to the generic risk factor terms (i.e. “risk factor”, “risks”, “health behaviours”, and “life styles”) utilized in the remaining reviews. A recent study compared two search strategies that relied on generic (e.g. “health status”, “morbidity”, etc.) or specific (e.g. “specific illnesses, such as ‘headache’, ‘epilepsy’, ‘diabetes mellitus’, etc.) search terms for health outcomes.¹³⁴ The study concluded that the different search strings “tended to identify different studies” and complete reliance on generic or specific search terms would likely introduce bias as studies are “missed” when relying on one strategy

alone.¹³⁴ While the study examined outcome related search terms, these findings may be extended to exposure search terms as well. If so, we would expect differences in the yield of primary studies when we compare reviews which solely relied on generic exposure search terms (e.g. “risk factor”) to those which incorporated smoking-specific search terms.

Reviews were also heterogeneous with respect to the comprehensiveness of the search strategy. The number of electronic databases searched ranged from one to four. As expected, the review⁹⁸ with the most comprehensive search strategy, which also involved a grey literature search, yielded the greatest number of studies (n=43). As described by Jadad et al., discordance across reviews is potentially explained by the comprehensiveness of the search as “reviews with more comprehensive search strategies are less likely to be biased”.⁹⁰ While differences in objectives and search strategies are potential explanations for discordance, these factors did not explain discordance across the identified reviews on smoking. Reviews with the lowest and highest yield of studies as well as those with different objectives (smoking-specific vs. unspecified exposures) consistently concluded that smoking was associated with an increased risk of AD.

Rather, the source of discordant conclusions is likely attributed to differential eligibility criteria. As demonstrated by the sensitivity analyses conducted by Almeida et al.⁹⁶, case-control and cohort studies reported effects in opposite directions. Consequently, eligibility criteria relating to study design was likely to impact review findings. The only review⁶¹ to conclude a protective association between smoking and AD was also the only review to solely rely on findings from case-control studies as cohort studies were unavailable. Reviews which solely included cohort studies^{20,62,63,64,97,99} or reported subgroup analyses restricted to cohort studies⁹⁸, consistently concluded that the evidence was suggestive of an increased risk of AD associated with smoking.

Jadad et al. also defined discordance as differences in the magnitude and statistical significance of meta-analytic results.⁹⁰ Two reviews^{97,99} reported pooled risk estimates for the association between current (versus never) smoking and AD. While both reported an increased risk of AD, the pooled estimate reported by Peters et al.⁹⁹ was slightly attenuated as compared to that reported by Anstey et al.⁹⁷ (*Peters et al.*⁹⁹ - HR: 1.59; 95% CI: 1.15, 2.20. *Anstey et al.*⁹⁷ – HR: 1.79; 95% CI: 1.43, 2.23). Variability with respect to the magnitude of the pooled risk estimate is likely attributed to reliance on different studies. While Anstey et al.⁹⁷ relied on only four studies for the analysis of current versus never smoking, Peters et al.⁹⁹ incorporated seven studies. The pooled analyses also differed with respect to the included studies. For example, both reviewers identified two publications reporting on the Washington Heights Medicare study. To avoid double counting

subjects, both reviewers opted to include only one of the two studies^{123,129} in the pooled analysis. However, the study chosen for inclusion differed across reviews. While Anstey et al. included the reporting by Merchant et al.¹²³ (RR: 1.70; 95% CI: 1.07, 2.71), Peters et al.⁹⁹ relied on the risk estimate reported by Luchsinger et al.¹²⁹ (RR: 2.70; 95% CI: 1.20, 6.30). Such variability may partially account for the difference in magnitude of the pooled risk estimates.

Discordance may also arise as a result of differential data extraction.⁹⁰ Reviewers may choose to extract continuous rather than categorical risk estimates or adjusted versus unadjusted risk estimates. As failure to adjust for potentially confounding variables may yield erroneously inflated or attenuated risk estimates¹³⁵, reliance on crude rather than maximally adjusted estimates may yield discordant conclusions. There was evidence of differential data extraction across systematic reviews reporting on smoking. To illustrate, five of the nine systematic reviews that abstracted data from the primary study reported by Merchant et al.¹²³ were compared. Four^{62,96,97,99} of the five systematic reviews extracted the adjusted risk estimate for current smoking (RR: 1.70; 95% CI: 1.10, 2.80) while one review⁹⁸ abstracted the crude risk estimate for the same exposure (RR: 1.90; 95% CI: 1.20, 3.00). While this difference was inconsequential, systematic differences across reviews with respect to data extraction may serve as a potential explanation for discordance.

Overlap across reviews

As recommended by White et al.⁵¹, the most recent review⁹⁸ with the highest yield of primary studies (43 studies reported in 40 publications) was used as the referent. As summarized in Tables 2a and 2b, when compared to the referent, the reviews by Patterson et al.⁶³ (n = 0) and Lee et al.⁶⁴ (n = 1) had the lowest number of overlapping studies. The degree of overlap was significantly higher in the review reported by Almeida et al.⁹⁶ with 60% overlap across reviews (26 studies reported in 25 publications). The remaining reviews included two to 10 overlapping studies.

The extent of primary study overlap is dependent on the methodological characteristics of the reviews, particularly, the search strategy and eligibility criteria.⁵¹ To identify explanations for the varying degree of overlap across reviews, the methodological characteristics of each review were compared to the referent⁹⁸. As expected, methodologically similar reviews were more likely to identify and include the same studies. The review⁹⁶ with the greatest number of overlapping studies shared methodological similarities with the referent. Both specifically sought smoking-related primary studies and both employed relatively broad eligibility criteria (i.e. inclusion of all case-

control or cohort studies reporting on the association between smoking and AD). The non-inclusion of a majority of the missed studies (13 of 17) can be attributed to publication date. More specifically, 13 studies (reported in 12 publications) that were included in the referent⁹⁸ but not included by Almeida et al.⁹⁶ were published after April 2000 and would not have been available for inclusion. Reasons for the non-inclusion of the remaining four studies (reported in three publications) is elusive but may be attributed to the search strategy, particularly, the lack of grey literature searching by Almeida et al.⁹⁶

A low degree of primary study overlap can be explained by methodological differences across reviews. As compared to the referent, reviews with very low ($n = 1$ to 3) primary study overlap did not specifically seek studies reporting on smoking. Rather, three^{62,63,64} reviews with low study overlap sought studies reporting on various exposures. As previously discussed, the objective of a review is likely to drive the search strategy. Compared to the referent, these reviews failed to incorporate smoking-related search terms. This may explain the differences in primary study yield and the low overlap between these reviews and the referent. Another review²⁰ with low overlap was essentially an update to a previous review and would have low overlap due to publication year limits (i.e. post 2005). While the referent review⁹⁸ and that reported by Peters et al.⁹⁹ both considered case-control and cohort studies, the low overlap between reviews is likely attributed to differences with respect to publication year restrictions. Eighteen studies included in the referent review⁹⁸ were ineligible for inclusion by Peters et al.⁹⁹ as they were published prior to 1996. Finally, important sources of methodological heterogeneity may explain the relatively low ($n=10$) primary study overlap identified in the Anstey et al.⁹⁷ review. While both Anstey et al.⁹⁷ and the referent review⁹⁸ specifically sought studies reporting on smoking, differences in eligibility criteria are likely to explain the non-inclusion of 33 studies. As compared to the referent, Anstey et al.⁹⁷ applied rigorous eligibility criteria. Case-control studies, cohort studies that did not adequately exclude prevalent cases at baseline, those with small sample sizes (i.e. <50 subjects), and those with a duration of follow-up less than one year were all excluded.⁹⁷ The strict eligibility criteria accounts for the non-inclusion of the 26 case-control studies included in the referent. Reasons for non-inclusion of the remaining studies may be attributed to other eligibility criteria or differences in the search strategy (e.g. lack of grey literature search).

Multiple reviews reporting on the same topic or clinical question results in unnecessary duplication of research efforts and waste of research resources.¹³⁶ While there was some overlap of primary studies across reviews, overlap of studies was relatively low when the review by Cataldo et

al.⁹⁸ was employed as the referent. However, when we compare the reviews by Anstey et al.⁹⁷ (n=10) and Peters et al.⁹⁹ (n=11), which were published within one year of each other, there is significant overlap with six common studies across reviews. As expected, the main conclusions of both reviews were concordant. Finally, as Patterson et al.⁶³ relied on the systematic review reported by Almeida et al.⁹⁶, there was complete overlap across these two reviews. Extensive primary study overlap emphasizes the “redundancy” of multiple reviews examining the same research question.¹³⁶

Overall findings

Considered cumulatively, the identified systematic reviews yielded relatively consistent findings suggesting an increased risk of AD associated with smoking. However, the increased risk of AD was only apparent in current smokers. Former or ever smoking was not associated with AD. Failure to detect an association for former or ever smoking may be attributed to poorly defined exposure categories.^{97,99} These categories are likely to include subjects with diverse smoking histories with respect duration and cessation time.^{97,99} Such heterogeneity may impede the detection of an association between AD and former or ever smoking, if one exists.^{97,99}

A number of case-control studies detected a *reduced* risk of AD attributed to smoking. While these results may be indicative of an association, lending epidemiological evidence to the proposed neuroprotective effect of nicotine, these findings are likely attributed to sources of bias inherent in the methodological design of such studies.^{61,98} This assumption is confirmed when findings of case-control studies are compared to those derived from methodologically rigorous prospective studies.⁹⁸ The review by Cataldo et al.⁹⁸ provided further confirmation suggesting that results derived from case-control studies were statistically different than those derived from cohort studies.⁹⁸ Of particular importance, case-control studies are susceptible to recall bias as exposure ascertainment is reliant on the ability to accurately recall past exposures.^{71,98} Differential recall across outcome categories may yield biased results.⁷²

Inadequate selection of a control population may also contribute to the findings derived from case-control studies.^{71,96} Although use of hospital controls has been cited as a method to reduce the potential for differential recall (i.e. to ensure that cases and controls have equal incentive to accurately recall past exposures), selection of hospital controls may give rise to selection bias.^{72,96,137} More specifically, because smoking is associated with a number of morbidities treated in

hospital/medical facilities, controls selected from such sources are likely to be exposed.^{96,137} This would result in an attenuated risk estimate.¹³⁷

Results of case-control and cohort studies may be susceptible to differential mortality or survival.^{61,96,98} Because smoking is associated with higher mortality rates, smokers are less likely to survive to an age suitable for recruitment in studies of geriatric conditions such as AD.^{57,138} Smokers that do survive to such an age may have characteristics (e.g. factors that confer genetic protection) that mitigate the adverse effects of smoking and/or protect against the development of AD.¹³⁸ Consequently, if smokers with such characteristics are compared to non-smokers, smokers would be less likely to develop AD resulting in risk estimates below 1.00.¹³⁸ Spurious results could also be obtained if deceased smokers were predisposed to AD.¹³⁸ The elimination of exposed ‘would-be cases’ from the sample would yield results suggesting that smokers are less likely to develop AD.¹³⁸

When the analysis is restricted to cohort studies, there is consensus regarding the detrimental association. The association was observed in the pooled analyses of cohort studies reported by Anstey et al.⁹⁷ and in the analysis restricted to industry unaffiliated cohort studies conducted by Cataldo et al.⁹⁸ Although Cataldo et al.⁹⁸ adjusted for the effect of industry affiliation, a factor that has shown to contribute to bias⁹⁸, the review by Anstey et al.⁹⁷ is strengthened by the exclusion of prevalent cases and stratification by smoking status (i.e. current, former, ever)²⁰. Exclusion of prevalent cases is imperative in prospective cohort studies as exposure status may be altered as a result of diagnosis.⁹³ Secondly, Anstey et al.⁹⁷ determined that current but not former or ever smoking was associated with AD. Because Cataldo et al.⁹⁸ did not distinguish between these smoking categories, the derived risk estimate is likely attenuated as it pertains to the effect of smoking considered as a broad category.

The current evidence pertaining to the effect of smoking on the risk of AD is limited by a number of factors. Available observational studies are heterogeneous with respect to the definition of former and ever smoking.^{97,99} Studies reporting on current smoking status and risk of AD may also be flawed. As neuropathological changes associated with AD maybe present decades before symptom onset, cohort studies that recruit subjects in mid- or late-life and examine current smoking status alone are likely to miss the critical exposure window.^{18,20} Reverse causation may explain the association as current smoking status may be altered by presence of disease. Further, current smoking status provides no indication of cumulative smoking history across the lifespan. As noted by several reviewers, pack-year smoking history would establish a more precise measure of smoking status.^{20,97,99} However, this information is largely unavailable in the current literature.^{97,99} Secondly,

most studies did not specify the type of smoking (i.e. cigarette, cigar, pipe) being considered. If the noxious properties are present in different concentrations, the health impact may differ. Differences across cigarette brands, cigarettes of the past versus those of the present, and regional differences may also impact study findings. Thirdly, the adverse health effects of smoking have been at the forefront of media attention. Because smoking is a behavioural risk factor and all of the observational studies relied on self-reported smoking history, there is potential for exposure measurement error (i.e. underreporting) due to the stigmatization of smoking in current society.¹³⁹ A study of head and neck cancer patients emphasized the necessity of objective measures for exposure ascertainment when examining the effect of smoking.¹⁴⁰ The potential for industry influence must also be considered when reviewing the available evidence.⁹⁸ To account for this potential source of bias, industry affiliation must be transparently reported.⁹⁸ As noted in a number of reviews, while the evidence suggests that smoking increases risk of AD, the isolated effect of nicotine is unknown.^{20,99} Finally, while there is evidence that the effect of smoking may be modified by APOE e4 status, further research is required to confirm the legitimacy of this interaction.²⁰

Table 2a - Smoking and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies^a	Results	Conclusion
Graves et al. ⁶¹ (1991)	Amstar score: 4 Publication Bias Assessed: No	To examine the effect of tobacco and alcohol consumption on the risk of AD.	All studies conducted before 1 January 1990	1. Medline	8	7 of 43	1. Ever vs. never smokers (n=8): (RR: 0.78; 95% CI: 0.62, 0.98) 2. Ever vs. never smokers (n=7)^b: (RR: 0.72; 95% CI: 0.56, 0.92) 3. Ever vs. never smokers subgroup analysis stratified by family history (n=7)*: (Positive family history – RR: 0.63; 95% CI: 0.41, 0.94. Negative family history – RR: 0.81; 95% CI: 0.58, 1.13) 4. Quantity of smoking (n=5)*: (<1 pack/day - RR: 0.80; 95% CI: 0.60, 1.07. >1 pack/day - RR: 0.66; 95% CI: 0.44, 1.00) 5. Pack-year smoking history (n=4): (<15.5 pack-years - RR: 0.73; 95% CI: 0.50, 1.09.	Smoking was associated with a reduced risk of AD.

							15.5-37.0 pack-years – RR: 0.63; 95% CI: 0.42, 0.95. >37.0 pack-years – RR: 0.50; 95% CI: 0.31, 0.80)	
Almeida et al. ⁹⁶ (2002)	Amstar score: 5 Publication Bias Assessed: No	To investigate the association between smoking and Alzheimer's disease.	All years from inception of the databases up to April 2000	1. Medline 2. PsychInfo	29	26 of 43	1. All case-control studies (n=21): (OR: 0.74; 95% CI: 0.66, 0.84; Test for statistical heterogeneity: p = 0.246) 2. Higher quality case-control studies (n=8): (OR: 0.82; 95% CI: 0.70, 0.97; Test for statistical heterogeneity: p = 0.279) 3. Higher quality case-control studies employing a matched-design: (OR: 0.82; 95% CI: 0.53, 1.27; Test for statistical heterogeneity: p = 0.283) 4. All cohort studies (n=6) (OR: 1.10; 95% CI: 0.94, 1.29; Test for statistical heterogeneity: p = 0.004) 5. Higher quality cohort studies (n=4): (OR: 1.12; 95% CI: 0.93, 1.34; Test for statistical heterogeneity: 0.308) 6. Cohort studies that "described the number of subjects who were smokers at	Association between smoking and AD was unclear.

							baseline and later developed AD" (n=2): (OR: 1.99; 95% CI: 1.33, 2.98; Test for heterogeneity: Not reported)	
Weih et al. ⁶² (2007)	Amstar Score: 6 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD.	January 1966 to June 2006	1. Medline 2. Embase 3. Cochrane Database 4. Current Contents	5	4 of 43	Three of five studies detected an increased risk of AD associated with current smoking. Two studies failed to detect an association between smoking and AD.	Evidence was suggestive of an increased risk of AD associated with smoking.
Patterson et al. ⁶³ (2007)	Amstar Score: 4 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD and other cognitive outcomes.	1966 to December 2005	1. Medline 2. Embase	0	0 of 43	Relied on the systematic review reported by Almeida et al. ⁹⁶	Evidence was suggestive of an increased risk of AD associated with smoking.
Anstey et al. ⁹⁷ (2007)	Amstar score: 4 Publication Bias Assessed: No	To examine the effect of smoking on risk of AD and other cognitive outcomes.	All years from inception of the databases to June 2005	1. PubMed 2. PsychInfo 3. Cochrane CENTRAL	10	10 of 43	1. Current smokers vs. Never smokers: (RR: 1.79; 95% CI: 1.43, 2.23; Test for statistical heterogeneity: $\chi^2 = 2.35$, 3df, $p = 0.50$) 2. Ever smokers vs. Never smokers: (RR: 1.21; 95% CI: 0.66, 2.22; Test for statistical heterogeneity: $\chi^2 = 12.19$ 2df, $p = 0.01$) 3. Former smokers vs. never smokers: (RR: 1.01; 95% CI:	Current smoking was associated with an increased risk of AD. Ever and former smoking showed no association with AD.

							0.83, 1.23; Test for statistical heterogeneity: $\chi^2 = 5.27$, 4df, $p = 0.26$) 4. Current smokers vs. former smokers: (RR: 1.70; 95% CI: 1.25, 2.31; Test for statistical heterogeneity: $\chi^2 = 1.85$, 3df, $p = 0.60$) 5. Current smokers vs. Former and Never smokers: (RR: 1.25; 95% CI: 0.49, 3.17; Test for statistical heterogeneity: $\chi^2 = 4.90$, 1df, $p = 0.03$)	
Peters et al.⁹⁹ (2008)	Amstar score: 6 Publication Bias Assessed: Yes, Funnel plots, No indication of publication bias	To examine the effect of smoking status and risk of all-cause dementia, AD, and cognitive decline.	1996 to November 2007	1. Medline 2. Embase 3. PsychInfo 4. Cochrane Database	11	9 of 43	1. Current smokers vs. Never smokers (n=8): (RR: 1.59; 95% CI: 1.15, 2.20; Test for statistical heterogeneity: Cochran Q = 23.35, $p = 0.0015$) 2. Former smokers compared to Never smokers: (RR: 0.99; 95% CI: 0.81, 1.23; Test for statistical heterogeneity: Cochran Q = 11.27, $p = 0.0804$)	Current smoking was associated with an increased risk of AD. No association between AD and former smoking.
Cataldo et al.⁹⁸ (2010)	Amstar score: 7 Publication Bias Assessed: Yes, Funnel plot, No evidence of publication bias	To investigate the association between cigarette smoking and Alzheimer's	Not specified	1. PubMed 2. PsychInfo 3. Cochrane CENTRAL 4. Google Scholar	43	Referent	1. Case-control studies without tobacco industry affiliation (n=18): (OR: 0.91; 95% CI: 0.75, 1.10; Test for statistical heterogeneity: $I^2=28.2\%$, $p=0.129$) 2. Case-control studies with	Smoking was associated with an increased risk.

		disease					tobacco industry affiliation (n=8): (OR: 0.86; 95% CI: 0.75, 0.98; Test for statistical heterogeneity: $I^2 = 0.0\%$, $p = 0.748$) 3. Cohort studies without tobacco industry affiliation (n=14): (RR: 1.45; 95% CI: 1.16, 1.80; Test for statistical heterogeneity: $I^2 = 70.0\%$, $p=0.000$) 4. Cohort studies with tobacco industry affiliation (n=3): (RR: 0.60; 95% CI: 0.27, 1.32; Test for statistical heterogeneity: $I^2 = 65.3\%$, $p = 0.056$)	
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of smoking	To examine the effect of several factors, including smoking, on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database Of Systematic Reviews	2	2 of 43	Results from one systematic review (Anstey et al.⁹⁷) and two additional cohort studies were discussed. - The identified systematic review suggests that current smoking is associated with an increased risk of AD. Former and ever smoking was not associated with AD. - Both cohort studies detected an increased risk of AD associated with current but not former smoking.	Evidence was suggestive of an increased risk of AD associated with current but not former smoking.

							Association between current smoking and AD was modified by APOE status (current smoking increased risk of AD in non-carriers only)	
Lee et al. ⁶⁴ (2010)	Amstar Score: 4 Publication Bias Assessed: No	To examine the effect of several factors, including smoking, on the risk of developing AD and other cognitive impairments.	All years up to August 2008	1. Pubmed 2. Embase 3. PsychInfo	4	1 of 43	All four included studies detected an increased risk of AD associated with smoking.	Smoking was associated with an increased risk of AD.

^a "Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent". Item adopted from *White, CM et al.*⁵¹

^b pooled analysis excluding outlying study

Table 2b - Overlap across reviews reporting on smoking and risk of AD

	Cataldo et al. ⁹⁸	Graves et al. ⁶¹	Almeida et al. ⁹⁶	Anstey et al. ⁹⁷	Weih et al. ⁶²	Patterson et al. ⁶³	Peters et al. ⁹⁹	Lee et al. ⁶⁴	Williams et al. ²⁰
Month/year published	04/2010	NR/1991	01/2002	03/2007	06/2007	10/2007	12/2008	03/2010	04/2010
Month/year of last search	NR	01/1990	04/2000	06/2005	06/2006	12/2005	11/2007	08/2008	10/2009
Design of included studies	Case-control, Cohort	Case-control	Case-control, Cohort	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort
Included primary studies:									
Heyman 1984	Yes	Yes	Yes	No	No	No	No	No	No
French 1985	Yes	Yes	Yes	No	No	No	No	No	No
Amaducci 1986	Yes	Yes	Yes	No	No	No	No	No	No
Chandra 1987	Yes	Yes	Yes	No	No	No	No	No	No
Shalat 1987	Yes	Yes	Yes	No	No	No	No	No	No
Barcley 1989	Yes	No	Yes	No	No	No	No	No	No
Katzman 1989	Yes	No	Yes	No	No	No	No	No	No
Grossberg 1989	No	No	Yes	No	No	No	No	No	No
Hofman 1989	No	Yes	No	No	No	No	No	No	No
Broe 1990	Yes	Yes	Yes	No	No	No	No	No	No
Ferini-Strambi 1990	Yes	No	Yes	No	No	No	No	No	No
Graves 1990	Yes	Yes	Yes	No	No	No	No	No	No
van Duijn 1991	Yes	No	Yes	No	No	No	No	No	No
Hebert 1992	Yes	No	Yes	No	No	No	No	No	No
Hirayama 1992	Yes	No	Yes	No	No	No	No	No	No
Brenner 1993	Yes	No	Yes	No	No	No	No	No	No
Prince 1994	Yes	No	Yes	No	No	No	No	No	No
Canadian Study of Health and Aging 1994	No	No	Yes	No	No	No	No	No	No
Plassman 1995	Yes	No	Yes	No	No	No	No	No	No
Forster 1995	Yes	No	Yes	No	No	No	No	No	No

Yoshitake 1995	Yes	No	No	Yes	Yes	No	No	No	No
Shaji 1996	Yes	No	Yes	No	No	No	No	No	No
Salib 1997	Yes	No	Yes	No	No	No	No	No	No
Lerner 1997	Yes	No	Yes	No	No	No	No	No	No
Wang 1997	Yes	No	Yes	No	No	No	No	No	No
Broe 1998	Yes	No	No	Yes	No	No	No	No	No
Harwood 1998*	Yes	No	No	No	No	No	No	No	No
Ott 1998	No	No	Yes	No	Yes	No	Yes	Yes	No
Wang 1999*	Yes	No	Yes	Yes	No	No	Yes	No	No
Merchant 1999	Yes	No	Yes	Yes	Yes	No	Yes	No	No
Launer 1999	Yes	No	Yes	Yes	Yes	No	Yes	No	No
Debanne 2000	Yes	No	No	No	No	No	No	No	No
Doll 2000	Yes	No	Yes	No	No	No	Yes	No	No
Bowirrat 2001	Yes	No	No	No	No	No	No	No	No
Lindsay 2002	Yes	No	No	Yes	Yes	No	Yes	No	No
Maia 2002	Yes	No	No	No	No	No	No	No	No
Bachman 2003*	Yes	No	No	No	No	No	No	No	No
Piguet 2003	Yes	No	No	No	No	No	Yes**	No	No
Tyas 2003	No	No	No	No	No	No	Yes	Yes	No
Moffat 2004	Yes	No	No	Yes	No	No	No	No	No
Juan 2004	Yes	No	No	Yes	No	No	Yes	No	No
Laurin 2004	Yes	No	No	Yes	No	No	No	No	No
Luchsinger 2005	Yes	No	No	Yes	No	No	Yes	No	No
Aggarwal 2006	Yes	No	No	No	No	No	Yes	No	Yes
Reitz 2007	Yes	No	No	No	No	No	Yes	Yes	Yes
Kivipelto 2008	No	No	No	No	No	No	No	Yes	No

*Publications reporting on multiple studies or presenting data for subgroups (treated as separate studies)

**Study was included in review but not for analyses of AD

NR = not reported; Yes = Included in review; No = Not included in review

Layout of table adopted from Siontin et al.¹³⁶

3.4 Polyunsaturated fatty acids

Research suggests that polyunsaturated fatty acids (PUFAs) may exert neuroprotective effects including the attenuation of cognitive decline and prevention of dementia.¹⁴¹ The neuroprotective effects are attributed to the role of PUFAs in mitigating cardiovascular risk factors associated with dementia, preventing inflammation, and decreasing the production of neuropathological hallmarks of AD, namely, beta-amyloid and neuritic plaques.¹⁴¹ Omega-3 (n-3) and omega-6 PUFAs can be obtained from several dietary sources including “dairy products, meat, vegetables, oils, and fish”.¹⁴¹ The effect of omega-6 and both long-chain (docosahexaenoic acid, eicosapentaenoic acid) and short-chain (alpha linolenic acid) omega-3 fatty acids on the incidence of AD have been examined in the literature with an emphasis on the effect of omega-3 fatty acids obtained from fish consumption.

Nine systematic reviews^{20,58,62,63,64,141,142,143,144} examining the association between polyunsaturated fatty acids and risk of AD were identified. Two^{58,141} of the reviews were deemed to be of low methodological quality according to the AMSTAR criteria and were consequently excluded from the complex review. Findings from the remaining seven moderate^{20,62,63,64,142,144} and high¹⁴³ quality reviews are qualitatively summarized.

a) Study: Issa et al.¹⁴²

Year: 2006

AMSTAR score: 7

Issa et al.¹⁴² reviewed the effect of omega-3 fatty acid intake on cognitive function and incidence of dementia. Several electronic databases were searched and bias was minimized through independent, duplicate screening and extraction.¹⁴² The reviewers identified three prospective cohort studies^{145,146,147} which examined the effect of omega-3 fatty acid on the development of AD. The studies observed an aggregate of 308 cases of AD (N = 7617) during periods of follow-up ranging from 2.1 to seven years. AD was diagnosed according to DSM and NINCDS-ADRDA criteria. All three studies estimated the intake of omega-3 fatty acids based on quantity of fish consumed. However, categorization of the exposure varied across the included studies with two studies^{145,147} examining the effect of weekly consumption and one¹⁴⁶ study examining the effect of daily consumption. In addition to examining the effect of omega-3 fatty acids derived from fish, one

study¹⁴⁷ also examined the effect of total omega-3 fatty acid, long-chain omega-3 fatty acids (docosahexaenoic acid, eicosapentaenoic acid) and short-chain omega-3 fatty acids(alpha linolenic acid) on incident AD.¹⁴² Heterogeneity across the included studies precluded a meta-analysis.¹⁴²

Two of three studies reported statistically significant findings suggesting a reduced risk of AD associated with fish consumptions ($\geq$ one time/week¹⁴⁵ - RR: 0.69; 95% CI: 0.47, 1.01. >18.5 g/day¹⁴⁶: RR: 0.30; 95% CI: 0.10, 0.90. >one serving/week¹⁴⁷ - RR: 0.40; 95% CI: 0.20, 0.90). Findings from one¹⁴⁷ of the studies also suggested that the highest quintile of intake of total n-3 fatty acid and DHA but not EPA or ALA was associated with a reduced risk of AD (*Total n-3 fatty acid 1.75g/day* - RR: 0.40; 95% CI: 0.10, 0.90. *DHA 0.10 g/day* - RR: 0.30; 95% CI: 0.10, 0.90. *ALA 1.46g/day* – RR: 0.70; 95% CI: 0.30, 1.60. *EPA 0.03 g/day* – RR: 0.90; 95% CI: 0.40, 2.30). This study also found that the association between total omega-3 fatty acid was modified by sex (p=0.02). Total intake of omega-3 fatty acids was associated with a reduced risk of AD in females but not males.¹⁴² The reviewers concluded that while there was some evidence of an association between omega-3 fatty acids and AD, the small number of available studies precluded definitive conclusions.¹⁴²

b) Study: Weih et al.⁶²

Year: 2007

AMSTAR score: 6

The effect of dietary fish consumption and omega-3 fatty acids on the incidence of AD was examined in the review by Weih et al.⁶² Dietary consumption was assessed by food frequency questionnaires across all included studies.⁶² Outcome ascertainment was achieved according to the NINCDS-ADRDA in all included studies.⁶² A pooled analysis of the identified evidence was not conducted.

The review identified the same three studies^{145,146,147} captured in the systematic review reported by Issa et al.¹⁴² (RRs presented in section a). Overall, two^{146,147} of the three included studies reported a statistically significant reduced risk of dietary fish consumption and one detected a protective effect associated with total n-3 fatty acids. Based on these results, the reviewers suggested that there was “good evidence” to support a reduced risk of AD associated with omega-3 fatty acids.⁶²

c) Study: Patterson et al.⁶³

Year: 2007

AMSTAR score: 4

The systematic review conducted by Patterson et al. examined the effect of several putative risk factors on the development of AD and other cognitive outcomes including unspecified dementia and vascular dementia.⁶³ Studies were located using a search of Medline, Embase, and by reviewing the reference list of pertinent studies.⁶³ Studies excluded by the primary reviewer were verified by three reviewers.⁶³ Duplicate, independent quality assessment and data extraction were carried out.⁶³ Longitudinal studies deemed to be of “fair” or “good” quality were eligible for inclusion.⁶³ Methodological quality was ascertained according to several criteria pertaining to the sampling strategy, exclusion of prevalent cases at baseline, completeness of follow-up, methods for exposure/outcome ascertainment, degree of confounding adjustment, and adequacy of the statistical analysis.⁶³ Only one relevant study¹⁴⁶ was identified. The study reported a reduced risk of AD associated with fish consumption exceeding 18.5 g/day (RR presented in section a).

d) Study: Lim et al.¹⁴³

Year: 2006

AMSTAR score: 10

The high-quality Cochrane systematic review conducted by Lim et al.¹⁴³ examined the association between omega-3 fatty acid and the risk of AD. An extensive electronic database search was conducted to identify studies randomized controlled trials published up to October 2006. The review identified zero studies.

e) Study: Dangour et al.¹⁴⁴

Year: 2010

AMSTAR score:5

The systematic review by Dangour et al.¹⁴⁴ examined the association between fish and polyunsaturated fatty acids and risk of AD. Six prospective cohort studies^{145,147,148,149,150,151} were eligible for inclusion. Two of the included studies^{145,147} were captured in earlier reviews^{62,142}. The six included studies observed an aggregate of 749 cases of AD (N = 12207) during periods of follow-up ranging from 3.9 to 21 years. A diagnosis of AD was based on NINCDS-ADRDA criteria in five of the included studies.¹⁴⁴ The criteria employed for outcome ascertainment in the remaining study¹⁴⁵ was not specified. Dietary intake of fish, polyunsaturated fatty acids (PUFA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) was measured by food frequency questionnaires (FFQs) in all six studies.¹⁴⁴ One study¹⁵⁰ also examined the association between AD and plasma concentrations of EPA and DHA. Heterogeneity across studies precluded a meta-analysis.¹⁴⁴

A total of four studies^{145,147,149,150} reported on the association between PUFA intake, estimated by fish consumption, and risk of AD. Of these studies, only one¹⁴⁷ reported a reduced risk of AD associated with higher fish consumption (RR for two studies^{145,147} reported in section a. ≥ 4 servings/week¹⁴⁹ – HR: 0.69; 95% CI: 0.91, 1.22. *Threshold undefined*¹⁵⁰ – No association; RR not reported in review, however, presented in section g).

Three studies^{147,148,151} investigated the association between AD and polyunsaturated fatty acids (PUFA) estimated by other or unspecified dietary sources and plasma levels. Two^{148,151} of the three studies reported no association between PUFA and AD (*Per SD increase*¹⁴⁸–HR: 1.07; 95% CI: 0.91, 1.25. *High intake from spreads*¹⁵¹ - No association; OR not reported in review). However, the latter study reported a reduced risk of AD associated with moderate PUFA consumption from spreads and risk of AD (OR: 0.40; 95% CI: 0.17, 0.94). One¹⁴⁷ study reported a decreased risk of AD associated with high omega-3 fatty acid intake (RR reported in section a).

Two studies^{147,150} investigated the association between subtypes of omega-3 fatty acids and risk of AD. One¹⁵⁰ found that both plasma concentrations and dietary intake of DHA were not associated with AD risk (*Plasma* - RR: 0.61; 95% CI: 0.31, 1.18. *Dietary* - RR: not reported). The other reported discrepant findings suggesting a reduced risk of AD associated with high DHA intake

(RR presented in section a). Plasma concentrations and dietary intake of EPA were not associated with risk of AD according to both studies (RR for one study¹⁴⁷ reported in section a. *Schaefer et al.*¹⁵⁰ - RR: not reported).

Overall, of the six included studies reporting on the association between PUFAs and AD, only one study reported a statistically significant reduced risk of AD associated with fish consumption, omega-3 fatty acids, and a high intake of DHA.¹⁴⁴ Based on these findings, the reviewers suggest the association between PUFAs and risk of incident AD was inconclusive.¹⁴⁴

f) Study: Lee et al.⁶⁴

Year: 2010

AMSTAR score: 4

The review by Lee et al.⁶⁴ examined the association between PUFAs and risk of AD. Methods for exposure and outcome ascertainment employed in the primary studies were not specified in the review.⁶⁴ Inclusion was restricted to studies of high methodological quality, which was established according to an assessment of several criteria, namely, sampling strategy, methods for exposure/outcome ascertainment, degree of confounding adjustment, and completeness of follow-up.⁶⁴ Heterogeneity across the included studies precluded a meta-analysis.⁶⁴

Two prospective cohort studies^{149,151} satisfied the eligibility criteria of the review. Both studies were captured by the review reported by Dangour et al.¹⁴⁴ The studies observed an aggregate of 266 cases of AD (N = 3682) during periods of follow-up ranging from nine to 21 years. One¹⁴⁹ reported a reduced risk of AD associated with higher fatty fish consumption (≥ 4 servings/week - HR: 0.54; 95% CI: 0.31, 0.95). The abstracted risk estimate differs from that reported in the review by Dangour et al.¹⁴⁴ An explanation for this discrepancy is provided in the discussion section (see page 94). The second included study reported a reduced risk of AD associated with moderate consumption of polyunsaturated fatty acid (RR presented in section e). The reviewers concluded that “there was consistent evidence of a protective effect of...fish consumption”.⁶⁴

g) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Technology Assessment prepared by the Duke Evidence-based Practice Center²⁰ collated evidence pertaining to the association between omega-3 fatty acids and risk of AD from longitudinal cohort studies. Previous systematic reviews were also eligible for inclusion. All included studies adhered to the NINCDS-ADRDA or DSM diagnostic criteria for AD ascertainment. Omega-3 fatty acid intake was ascertained based on the quantity of fish consumption, consumption of unspecified dietary sources or plasma/serum levels.²⁰ Exposure status was ascertained according to serum, plasma, blood, or erythrocyte membrane concentrations of PUFAs in four studies reported in five publications^{150,152,153,154,155}. Exposure ascertainment was achieved according to self-reported dietary histories and/or data derived from food frequency questionnaires (FFQs) in the remaining studies. Heterogeneity across included studies precluded a pooled analysis.

The HTA identified a systematic review¹⁴¹ which summarized evidence from seven longitudinal cohort studies reported in nine publications^{145,146,147,148,149,150,152,153,154}. Two studies^{155,156} published after the included review were identified and included. Six of the publications^{145,146,147,148,149,150} were captured in earlier systematic reviews. The nine studies, reported in 11 publications, observed an aggregate of 1233 cases of AD (N = 24966) during periods of follow-up ranging from 2.1 to 9.6 years.

Of the seven studies reporting on the effect of fish consumption, only three studies reported in five publications^{146,147,148,152,153} detected a statistically significant reduced risk of AD (RR for two studies reported in three publications^{146,147,148} presented in section a). However, one of these studies, reported in two publications^{152,153}, reported a reduced risk of AD associated with moderate but not high fish consumption (*2 to 3 times a week* - HR: 0.59; 95% CI: 0.37, 0.94. *≥ 4 times per week* - HR: 0.58; 95% CI: 0.25, 1.34). Four^{145,149,150,156} of the remaining studies failed to detect a statistically significant association between fish consumption and risk of AD (RRs for two studies^{145,149} presented in sections a and e. *≥ 2 times/week*¹⁵⁰: RR: 0.61; 0.28, 1.33. *High versus no intake*¹⁵⁶ - HR: 0.99; 95% CI: 0.76, 1.29).

Conflicting findings were obtained from the analysis of PUFAs derived from other or unspecified dietary sources or ascertained according to plasma/serum levels.²⁰ One study each reported no association between omega-3 consumption¹⁵⁶ (RR not reported in review) and plasma concentrations of total PUFA¹⁵⁵ (HR: 1.12; 95% CI: 0.63, 1.98). Two studies, reported in three publications, found no association between higher linoleic^{146,148} or linolenic¹⁴⁷ acid consumption with AD (*> 15g/day*^{146,148} - RR: 0.60; 95% CI: 0.30, 1.20. RR for one study¹⁴⁷ presented in section a).

One¹⁴⁷ of four studies examining DHA reported a reduced risk of AD associated with higher dietary intake (RR presented in section a). The remaining studies^{150,155,156} reported no association between AD and dietary intake or plasma concentrations of DHA (RR for one study¹⁵⁰ presented in section e. RRs for two studies^{155,156} not reported in review). Plasma concentrations of EPA were associated with a reduced risk of AD/dementia according to one study reported in two publications^{152,153} (RR not reported in review). However, total or dietary intake of EPA was not associated with AD according to three studies^{147,155,156} (RR for one study¹⁴⁷ presented in section a. RRs for two studies^{155,156} not reported in review). Although not presented in the HTA report, the review reported by Dangour et al.¹⁴⁴ indicated that one additional study¹⁵⁰ found no association between plasma concentrations of EPA and AD (see section e).

Considered cumulatively, the reviewers concluded that the evidence was not suggestive of an association between PUFAs and risk of AD.²⁰

Discussion

Seven higher quality systematic reviews collating evidence from 12 longitudinal studies reporting on the association between PUFAs and risk of AD were identified and included. The systematic reviews^{62,64,142} including the fewest number of studies consistently concluded that there was evidence to suggest that PUFAs may protect against the development of AD. However, larger systematic reviews conducted by Williams et al.²⁰ and Dangour et al.¹⁴⁴ identified a number of negative studies suggesting that there was insufficient evidence to suggest an association between PUFAs and risk of AD.^{20,144}

Non-independence of the included systematic reviews, due to significant primary study overlap, must be noted. Seven of the eleven available primary studies appeared in more than one review. Using the review by Williams et al.²⁰ as the referent, primary study overlap varied from zero¹⁴³ to five¹⁴⁴ studies. All of the studies identified by Issa et al.¹⁴², Weih et al.⁶², and Patterson et al.⁶³ were also captured in the referent. Further, the referent and Dangour et al.¹⁴⁴ shared all but one¹⁵¹ of the six studies included in the latter review. Despite reliance on the same primary studies, there was evidence of discrepant data abstraction across reviews. For example, two^{20,144} of the three reviews which included the primary study by Huang et al.¹⁴⁹, relied on the fully adjusted risk estimate which showed no association (HR: 0.69; 95% CI: 0.91, 1.22). The remaining review⁶⁴

abstracted the minimally adjusted risk estimate which showed a statistically significant association between high fish consumption and risk of AD (HR: 0.54; 95% CI: 0.31, 0.95). Similarly, data abstracted from a second primary study¹⁵¹ differed across reviews. While one review¹⁴⁴ relied on the fully adjusted risk estimate for the second quartile of consumption (OR: 0.53; 95% CI: 0.21, 1.37), another review⁶⁴ relied on the minimally adjusted risk estimate for the third quartile (OR: 0.54; 95% CI: 0.31, 0.95). These examples illustrate that systematic differences in data abstraction may contribute to discordant conclusions across reviews which rely on the same primary studies.⁹⁰

The inconsistent findings across primary studies may be attributed to a number of factors, particularly pertaining to issues associated with exposure ascertainment.^{20,142} As noted by Issa et al., studies examining the effect of PUFAs are limited by a “lack of standardized methods to measure nutrient levels” which may give rise to exposure measurement error resulting in biased risk estimates.¹⁴² A number of primary studies employed food frequency questionnaires (FFQs) to ascertain dietary intake. Although FFQs are widely used, evidence suggests FFQs are likely to underestimate the true association which may explain the number of studies reporting null findings.¹⁵⁷ Heterogeneity with respect to the source and quantity of PUFAs under investigation may also contribute to the inconsistent findings across primary studies.^{20,142} More specifically, some studies examined PUFAs from various dietary sources, some restricted the analysis to PUFAs obtained from fish consumption, while others also included intake from supplements.^{20,142} Moreover, some studies examined serum or plasma concentrations of PUFAs while others solely examined dietary intake. There was also heterogeneity across studies examining the effect of PUFAs estimated by fish intake.^{20,142} More specifically, there was variation in the “types of fish (e.g. fatty versus non-fatty)” and in the “methods of preparation” (fried vs. other).^{20,142}

Additional sources of methodological heterogeneity may have also contributed to the divergent findings across primary studies. Diet is associated with other putative protective factors for AD.¹⁴² For example, higher PUFA consumers may also adhere to other healthy behaviours which may confound the association between the variables of interest.¹⁴² Although a majority of the included studies adjusted for potentially confounding variables, variability in the degree of confounding adjustment across the included studies may have given rise to methodological heterogeneity resulting in inconsistent findings.

Overall, although smaller scale reviews have concluded that PUFAs were associated with AD, findings from recent methodologically sound systematic reviews collating evidence from a larger number of studies have failed to yield consistent findings. Inconsistent findings across

primary studies emphasize the need for randomized controlled trials, larger prospective cohort studies, and standardized methods for exposure ascertainment.^{20,142,144}

Table 3 – Polyunsaturated fatty acids (PUFAs) and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies^a	Results	Conclusion
Issa et al. ¹⁴² (2005)	Amstar Score: 7 Publication Bias Assessed: No	To investigate the association between omega-3 fatty acid consumption and cognitive function, AD, and dementia.	All years up to 2003	1. Medline 2. Embase 3. PreMedline 4. Cochrane Central Register of Controlled Trials 5. Dissertation abstracts (OVID interface) 6. CAB Health	3	3 of 9	1. Fish consumption: Two of three studies detected a significant reduced risk of AD associated with fish consumption. 2. Total Omega-3 Fatty Acid, Alpha-linolenic acid (ALA), Docosahexaenoic acid (DHA), and Eicosapentaenoic acid (EPA): DHA but not ALA or EPA were protective against AD in the only study to report on these exposures. Total omega-3 fatty acid consumption was beneficial in females	Some evidence of an association; further research is necessary to arrive at a definitive conclusion

							only.	
Lim et al. ¹⁴³ (2006)	Amstar Score: 10 Publication Bias Assessed: Reviewers intended to test for publication bias, however, no studies were eligible for inclusion	To investigate the association between omega-3 fatty acid and dementia	All years from inception of the databases to October 2005.	1. Medline 2. Embase 3. Cinahl 4. PsychInfo 5. The Cochrane Dementia and Cognitive Improvement Group's Specialised Register 6. CENTRAL (Cochrane Library issue 3, 2005) 7. AMED 8. ClinicalTrials.gov 9. NRR (National Research Register)	0	0 of 9	Zero studies (RCTs) satisfied the inclusion criteria of the review under analysis	No evidence

				10. Copernic 11. Google 12. AgeLine Databases 14. Alt-Health Watch 15. Biological Abstracts 16. BioMed Central 17. Clinical Pharmacology Database 18. DIMDI 19. Dissertation Abstracts 20. HerbMed 21. HSTAT (Health Services Technology Assessment Text) 22. Web of Science				
Weih et al. ⁶² (2007)	Amstar Score: 6 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD.	January 1966 to June 2006	1. Medline 2. Embase 3. Cochrane Database 4. Current Contents	3	3 of 9	1. Fish consumption: Two of three studies detected a significant reduced risk of AD associated with fish consumption. 2. Omega-3 fatty acids: The only study to report on total omega-3 fatty acid	PUFAs may exert a protective effect.

							detected a protective effect.	
Patterson et al. ⁶³ (2007)	Amstar Score: 4 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD and other cognitive outcomes.	1966 to December 2005	1. Medline 2. Embase	1	1 of 9	The only identified study reported a reduced risk of AD associated with fish consumption exceeding 18.5 g/day (RR: 0.30; 95% CI: 0.10, 0.90)	Fish consumption appeared to protect against dementia; no conclusions drawn for AD specifically
Dangour et al. ¹⁴⁴ (2010)	Amstar score: 5 Publication Bias Assessed: No	To examine the effect of PUFAs and other dietary exposures on risk of AD	Not specified. Databases accessed on July 2007.	1. PubMed 2. Embase 3. Cochrane Library	6	5 of 9	1. Fish consumption: Only one out of four included studies detected a significant association (≥ 2 servings/week - RR: 0.40; 95% CI: 0.20, 0.90). 2. Polyunsaturated fatty acids (PUFA): One of three studies reporting on polyunsaturated fatty acids detected a reduced risk of AD. 3. PUFA subtypes:	Association between PUFAs and risk of AD was inconclusive

							Of the two studies reporting on the effect of PUFA subtypes, both failed to detect an association between EPA and AD. One detected a protective effect of DHA (RR: 0.30; 95% CI: 0.10, 0.90).	
Lee et al. ⁶⁴ (2010)	Amstar Score: 4 Publication Bias Assessed: No	To examine the effect of several factors on the risk of developing AD and other cognitive outcomes.	All years up to August 2008	1. Pubmed 2. Embase 3. PsychInfo	2	1 of 9	Both studies reporting on the risk of AD associated with PUFAs detected an association	“There was consistent evidence of a protective effect of...fish consumption”
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of PUFAs	To examine the effect of several factors, including PUFAs, on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	9	Referent	1. Fish consumption: Three of seven studies detected a protective effect. 2. Total PUFAs and PUFA subtypes: Of the seven studies, majority reported null results. One of four studies reported a reduced risk of AD associated with DHA. Plasma EPA was associated with a protective effect in one study. Three studies failed to detect an association between	PUFAs were not associated with AD.

							dietary EPA and AD.	

^a“Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent”. Item adopted from *White, CM et al.*⁵¹

3.5 Folate

The association between folate, a B vitamin, and risk of AD, has been attributed to its effects on homocysteine concentrations.^{158,178} Research suggests that elevated plasma homocysteine, a neurotoxic amino acid and putative cerebrovascular risk factor, is associated with an elevated risk of AD.^{158,178} Involved in the “conversion of homocysteine to methionine”, higher serum folate has been associated with lower homocysteine levels.^{158,178} Further, the antioxidant properties of folic acid has been implicated as a possible explanation for its purported association with AD.¹⁵⁹

Six systematic reviews^{20,58,62,64,144,169} reporting on the effect of folate were identified. One⁵⁸ review was of low methodological quality and was excluded. Results from five moderate quality reviews, which included fourteen primary studies^{160,161,162,163,164,165,171,172,173,174,175,176,177,178} are presented below.

a) Study: Raman et al.¹⁶⁹

Year: 2007

AMSTAR score: 5

The effect of folate and risk of AD was examined by Raman et al.¹⁶⁹ Two electronic databases were searched (Medline and Commonwealth Agricultural Bureau Abstracts). Inclusion was restricted to cohort and case-control studies which adequately distinguished between AD and all-cause dementia. A total of eleven studies were identified and included. Six cohort studies^{161,163,172,173,174,175}, which observed an aggregate of 499 cases of AD (N=3779) over a period of follow-up ranging from three to eight years, were included. The remaining five case-control studies^{160,162,164,165,171} included a total of 557 cases and 563 controls.

Nine studies^{160,161,162,163,164,171,172,173,174} examined the association between blood folate levels and AD. Four^{162,164,171,172} of nine studies reported an increased risk of AD associated with low blood folate levels (RRs not reported in review). Only two studies^{165,175} reported on dietary folate intake. One¹⁶⁵ detected an association between low folate intake and AD while the other reported that there was no association (RRs not reported in review). The authors concluded that the association between dietary intake and risk of AD was unclear. The association between low blood folate and AD was also deemed inconclusive due to heterogeneity across studies with respect to defining exposure status.¹⁶⁹

b) Study: Weih et al.⁶²

Year: 2007

AMSTAR score: 6

The effect of folate was examined in the review by Weih et al.⁶² Medline, Embase, Current Contents, and the Cochrane databases were searched for relevant literature.⁶² The search was supplemented by a review of www.clinicaltrialresults.org and of reference lists of pertinent papers. The review was restricted to longitudinal studies of disease-free populations.⁶² The Oxford Centre for Evidence-based Medicine criteria, which evaluates the strength of evidence for a given risk factor based on the methodological design of available studies, was used.⁶² The only included study¹⁷⁴ observed 60 incident cases of AD (N=370) over a follow-up of three years. The study reported an increased risk of AD associated with low serum folate (*Folate* ≤ 10 nmol/l versus normal B12 and folate levels - RR: 2.10; 95% CI: 1.20, 3.50). No conclusions were drawn by the reviewers regarding the association between folate and risk of AD.

c) Study: Dangour et al.¹⁴⁴

Year: 2010

AMSTAR score: 5

The systematic review by Dangour et al. examined the association between several nutrients, including folate, and risk of AD.¹⁴⁴ PubMed, Embase, and the Cochrane Library were searched. Inclusion was restricted to clinical trials and prospective cohort studies. Included studies employed the DSM-III, DSM-IV, ICD-10, and NINCDS-ADRDA criteria for outcome ascertainment. Exposure status was ascertained according to serum or plasma nutrient levels, food diaries, and food frequency questionnaires.¹⁴⁴ A pooled analysis was not conducted.

A total of eight cohort studies^{161,172,173,174,175,176,177,178} investigating the association between serum folate levels or folate intake and risk of AD were identified. The studies observed an aggregate of 704 cases of AD (N=5182) over a duration of follow-up ranging from three to 9.3 years. Of the five studies investigating the association between serum folate levels and AD, only one study

detected an association ($\leq 11.8 \text{ nmol/l}^{172}$ - HR: 1.98; 95% CI: 1.15, 3.40. *19.0 versus 16.4 nmol/l*¹⁷⁶ – No association; OR not reported in review. ‘*Low folate*’¹⁷³ – No association; RR not reported in review. $\leq 10 \text{ nmol/l}^{174}$ – RR: 1.70; 95% CI: 0.90, 3.20. *Lowest quartile versus highest*¹⁶¹ – OR: 2.17; 95% CI: 0.85, 5.53).

Two of three studies reported an association between high folate intake and a reduced risk of AD ($\geq$ *Reference dietary allowance versus < Reference dietary allowance*¹⁷⁷ - RR: 0.41; 95% CI: 0.22, 0.76. *487.9 $\mu\text{g/day}$ versus 292.9 $\mu\text{g/day}$* ¹⁷⁸ - HR: 0.50; 95% CI: 0.30, 0.90. *Highest quintile versus lowest*¹⁷⁵ - OR: 1.60; 95% CI: 0.50, 5.20). The reviewers concluded that the association between folate and risk of AD was inconclusive.

d) Study: Lee et al.⁶⁴

Year: 2010

AMSTAR score: 4

The review by Lee et al. examined several putative risk factors associated with AD.⁶⁴ PubMed, Embase, and PsychInfo were searched for pertinent studies. Inclusion was restricted to longitudinal studies of high methodological quality. Quality was ascertained according to an assessment of several criteria, namely, sampling strategy, methods for exposure/outcome ascertainment, degree of confounding adjustment, and completeness of follow-up. Two cohort studies^{161,172}, which observed an aggregate of 119 cases (N=1042) over a duration of follow-up ranging from 3.8 to five years, were included. Only one¹⁷² of the two studies reported an increased risk of AD associated with low serum folate concentrations (HR/RRs reported in section c). Based on these findings, the reviewers concluded that the evidence was “inconsistent”.⁶⁴

e) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Health Technology Assessment (HTA), prepared for the US Agency for Healthcare Research and Quality, examined the effect of folate on the risk of AD.²⁰ Outcome ascertainment was achieved according to DSM or NINCDS-ADRDA criteria. The exposure was ascertained according to serum folate concentrations or food frequency questionnaires.²⁰

Four cohort studies, which observed an aggregate of 483 cases of AD (N=3192) over a duration of follow-up ranging from three to 6.1 years, were included. As reported by the reviewers, both^{172,174} studies reporting on serum folate detected an increased risk of AD associated with low concentration (HR for one study¹⁷² reported in section c. ≤ 10 nmol/l versus ≥ 10 nmol/l¹⁷⁴ - HR: 1.80; 95% CI: 1.00, 3.40). One¹⁷⁸ of two^{175,178} studies examining total folate intake reported a statistically significant reduced risk of AD associated with high intake (HR/RR for both studies reported in section c).

According to the reviewers, low folate serum concentrations appeared to be associated with an increased risk of AD, although the strength of evidence was deemed low. The association between total (dietary and supplements) folate intake and AD was inconclusive.²⁰ The reviewers concluded that the small number of studies necessitates further research.²⁰

Discussion

Across reviews, the number of primary studies identified varied from one to nine. The review¹⁶⁹ that identified the highest number of primary studies employed a more inclusive approach with respect to eligible study designs. Compared to the other four reviews, which restricted inclusion to cohort studies, Raman et al.¹⁶⁹ also included five^{160,162,164,165,171} case-control studies. Secondly, reviews which examined multiple putative factors^{62,64} tended to identify fewer primary studies as compared to those that specifically sought evidence pertaining to B vitamins^{144,169}. As the objectives differed across reviews, so did the search strategies. Reviews which aimed to collate

evidence on several risk factors^{62,64} failed to incorporate risk factor-specific search terms (e.g. “folate”). Rather, these studies relied on generic terms such as “risk factor”, “risks”, “health behaviours”, or “lifestyles”. In contrast, reviews which specifically sought studies on folate tended to incorporate risk factor-specific search terms (e.g. B9, folic, folate, folinic, leucovorin, methyltetrahydrofolate, pteroylglutamic).^{144,169} As previously discussed, reliance on generic versus specific exposure search terms may yield “different studies”.¹³⁴ As such, this methodological difference may explain variability across reviews with respect to primary study yield.

Comparing reviews reporting on the association between folate and AD highlights important limitations with respect to quality assessment instruments. Like other quality assessment tools, AMSTAR assesses quality of reporting rather than true methodological quality.⁵¹ For example, reviews which adequately report details regarding the search strategy (e.g. report databases and years searched, provide search terms and strategy, and indicate that search was “supplemented” with search of bibliographies, reviews, or other means etc.) would earn a score for the appropriate AMSTAR item. AMSTAR does not require an assessment of the quality of the search strategy. Quality appraisers are not required to assess the adequacy of the keyword and medical subject headings, the electronic databases searched, or the range of years searched. As such, reviews with low and high primary study yields (due to poor versus comprehensive search strategies) may score equivalently if they adequately report details of the search. Comparing the reviews with the highest¹⁶⁹ and lowest⁶² primary study yield suggests that thoroughness of reporting drives the AMSTAR score irrespective of quality. Weih et al.⁶² identified a single study reporting on folate while Raman et al.¹⁶⁹ identified eleven studies, five of which employed a case-control design. Weih et al.⁶² restricted inclusion to cohort and experimental studies. As such, we would expect six of the prospective cohort studies captured by Raman et al.¹⁶⁹ to also be included by Weih et al.⁶² as both reviews considered the same range of years (1966-2006) and applied relatively similar and broad eligibility criteria (e.g. studies reporting specifically on AD, those that provided a measure of association, etc.). However, only one of the six cohort studies was identified by Weih et al.⁶² The authors themselves have suggested that the search may not have been comprehensive and that “extending of the search term probably would bring up more studies that are relevant”.⁶² However, since the reviewers adequately reported the search string and other search-related details, the review was awarded a point for the relevant AMSTAR item. Although the search conducted by Raman et al.¹⁶⁹ appeared to be more comprehensive, as suggested by the higher yield, the reviewers failed to provide the full search string. Consequently, Weih et al.⁶² scored one point higher than Raman et

al.¹⁶⁹ on the AMSTAR tool. However, the higher score is not necessarily indicative of higher study quality. Rather, the higher score is attributed to greater thoroughness of reporting.

There was evidence of differential data extraction across reviews. For example, different risk estimates were extracted from the primary study reported by Wang et al.¹⁷⁴. Dangour et al.¹⁴⁴ relied on the adjusted risk estimate corresponding to folate levels ≤ 10 nmol/l versus ≥ 10 nmol/l (RR: 1.70; 95% CI: 0.90, 3.20). In contrast, Weih et al.⁶² extracted data for the comparison of low folate levels (≤ 10 nmol/l) versus normal levels of both B12 and folate (RR: 2.10; 95% CI: 1.20, 3.50). Further, Williams et al.²⁰ relied on the crude risk estimate for folate levels ≤ 10 nmol/l versus ≥ 10 nmol/l (RR: 1.80; 95% CI: 1.00, 3.40). Depending on the risk estimate extracted, reviewers reached discordant conclusions with respect to the primary study in question. For example, Raman et al.¹⁶⁹ and Dangour et al.¹⁴⁴ concluded that results of the study were suggestive of a lack of an association between folate levels and AD. In contrast, Weih et al.⁶² and Williams et al.²⁰ concluded that the study contributed evidence of an association.

When all five reviews are considered, there was significant primary study overlap with six studies appearing in more than one review. Using the review by Dangour et al.¹⁴⁴ as the referent, all of the studies identified by Williams et al.²⁰, Weih et al.⁶², and Lee et al.⁶⁴ were included in the referent review. Five of the studies identified by Raman et al.¹⁶⁹ were also included by Dangour et al.¹⁴⁴ As expected with such primary study overlap, the conclusions of the reviews were relatively consistent. The identified systematic reviews concluded that the association between serum folate concentrations or folate intake with AD was unclear or inconclusive. One review²⁰ noted that there was some evidence of an association between low serum folate and AD. However, the reviewers cautioned that the strength of evidence was weak. As recommended, future primary studies need to employ consistent folate exposure categories or thresholds to allow for meaningful synthesis.¹⁶⁹

Table 4 – Folate and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies^a	Results	Conclusion
Raman et al. ¹⁶⁹ (2007)	Amstar Score: 5 Publication Bias Assessed: No	To examine the effect of vitamin B-6, vitamin B-12, and folate on AD and other cognitive outcomes.	1966 to November 2006	1. Medline 2.Commonwealth Agricultural Bureau Abstracts	11	5 of 8	1. Serum/plasma concentrations: Three of nine studies detected an association between blood folate levels and risk of AD. 2. Dietary intake: One of two studies detected an association between low folate intake and incident AD.	Folate intake – Association unclear. Blood folate – Association inconclusive due to heterogeneity.
Weih et al. ⁶² (2007)	Amstar Score: 6 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD.	January 1966 to June 2006	1. Medline 2. Embase 3. Cochrane Database 4. Current Contents	1	1 of 8	The only identified study detected an increased risk of AD associated with low folate (RR: 2.10; 95% CI: 1.20, 3.50).	No conclusion drawn by authors.

Dangour et al. ¹⁴⁴ (2010)	Amstar score: 5 Publication Bias Assessed: No	To examine the effect of B-vitamins and other dietary exposures on risk of AD	Not specified. Databases accessed on July 2007.	1. PubMed 2. Embase 3. Cochrane Library	8	Referent	1. Serum/plasma concentrations: One of five studies detected an increased risk of AD associated with low serum folate. 2. Dietary intake: Two of three studies detected an association between folate intake and risk of AD.	Association between folate and risk of AD was unclear.
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of folate	To examine the effect of several factors, including folate, on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	4	4 of 8	1. Serum/plasma concentrations: One of two studies detected an increased risk of AD associated with low serum folate. Second study detected a marginally significant increased risk. 2. Total intake: One of two studies detected a reduced risk of AD associated with high total folate intake.	Low serum folate may be associated with an increased risk of AD. Small number of studies necessitates further research.
Lee et al. ⁶⁴ (2010)	Amstar Score: 4 Publication Bias Assessed: No	To examine the effect of several factors on the risk of developing AD and other cognitive outcomes.	All years up to August 2008	1. Pubmed 2. Embase 3. PsychInfo	2	2 of 8	One of two studies detected an increased risk of AD associated with low serum folate (HR: 1.98; 1.15, 3.40)	Available evidence was inconsistent.

^a“Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent”. Item adopted from White et al.⁵¹

3.6 Other micronutrients

Dietary deficiencies, “beginning in middle age or late adult life”, may impact the etiological process of AD or dementia.¹⁴⁴ A number of micronutrients are purported protective factors against AD. As with folate, other B vitamins are believed to reduce the risk of AD as a result of their effect on homocysteine concentrations.^{158,178} Research suggests that B vitamins (i.e. folate, vitamin B6, vitamin B12) may lower plasma homocysteine, a neurotoxic amino acid, associated with AD.^{158,178} Subsequent decreases in cerebral damage, particularly in regions associated with AD, have also been detected.¹⁶⁶ One important exception is niacin (vitamin B3), which at higher doses has shown to increase homocysteine levels in animals and humans.¹⁶⁷ However, niacin deficiencies have been linked to pellagra, a condition which is believed to cause dementia.¹⁵⁹ The association between vitamins C and E, flavonoids, and beta-carotene with risk of AD has been attributed to their antioxidant activity.¹⁶⁸ There is evidence to suggest that these micronutrients reduce oxidative stress attributed to “beta-amyloid accumulation”, a feature of AD pathophysiology.¹⁶⁸

Nine systematic reviews^{20,58,59,62,63,64,144,169,170} examined the association between micronutrients (i.e. vitamin B6, vitamin B12, vitamin B3, vitamins C and E, multivitamins, flavonoid, beta-carotene) and risk of AD. Three reviews^{58,59,170} were excluded due to low methodological quality.

3.6.1 Vitamin B12

a) Study: Raman et al.¹⁶⁹

Year: 2007

AMSTAR score:5

The effect of B-vitamins on the risk of AD was examined by Raman et al.¹⁶⁹ Inclusion was restricted to cohort and case-control studies which adequately distinguished between AD and all-cause dementia. The review included five cohort studies which observed an aggregate of 450 cases of AD (N=3553) over a follow-up period ranging from three to eight years. Four case-control studies, which included a total of 493 cases and 499 controls, were also included.

The reviewers identified four case-control^{160,162,164,171} and four cohort^{163,172,173,174} studies which examined the association between blood concentrations of vitamin B12 and risk of AD. Seven studies failed to detect an association (OR/RRs not reported in review). The remaining case-control study¹⁷¹ detected an increased risk of AD associated with low vitamin B 12 concentration (<200 versus >280 pmol/l: OR not reported). One cohort study¹⁷⁵ reported on the association between dietary intake of B-12 and AD. The study did not detect an association (RR not reported in review). Based on these findings, the reviewers concluded that the evidence was not suggestive of an association between vitamin B-12 and AD.¹⁶⁹

b) Study: Dangour et al.¹⁴⁴

Year: 2010

AMSTAR score: 5

The systematic review by Dangour et al.¹⁴⁴ examined the association between several nutrients, including vitamin B-12, and risk of AD. Included studies employed the DSM-III, DSM-IV, ICD-10, and NINCDS-ADRDA criteria for outcome ascertainment. Exposure status was ascertained according to serum or plasma nutrient levels, food diaries, and food frequency questionnaires.¹⁴⁴ Heterogeneity across the included studies precluded a meta-analysis. The review included seven cohort studies, which observed an aggregate of 655 cases of AD (N=4956) over a period of follow-up ranging from three to 9.3 years.

Four cohort studies^{172,173,174,176} examined the association between vitamin B 12 serum/plasma concentrations and AD. All four studies failed to detect an association (275 versus 305 pmol/l¹⁷⁶ – No association; OR not reported. ≤ 150 pmol/l¹⁷⁴ – RR: 1.60; 95% CI: 0.90, 2.80. ‘Low vitamin B12’¹⁷² – HR: 0.66; 95%CI: 0.40, 1.09. ‘Vitamin B12 levels’¹⁷³ – No association; RR not reported).

Three cohort studies^{175,177,178} examined the association between dietary intake (food and supplements) of vitamin B-12 and AD risk. Higher dietary intake of vitamin B-12 was not associated with risk of AD according to all three studies ($\geq$ reference dietary allowance versus < reference dietary allowance¹⁷⁷ – RR: 0.60; 95% CI: 0.26, 1.36. >13.5 versus <3.5 μ g/day¹⁷⁸ – HR: 1.10; 95% CI: 0.70, 1.70. Highest versus lowest quintile¹⁷⁵ – OR: 0.60; 95% CI: 0.20, 1.60). Considered cumulatively, the reviewers concluded that the association between B-vitamins and AD was inconclusive.¹⁴⁴

c) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Health Technology Assessment (HTA), prepared for the US Agency for Healthcare Research and Quality, examined the effect of medical, social/behavioural, environmental, dietary, and pharmacological factors on the risk of AD.²⁰ One of the many dietary factors examined in the review was the effect of vitamin B-12. Outcome ascertainment was achieved according to DSM or NINCDS-ADRDA criteria. The exposure was ascertained according to serum nutrient levels and responses to food frequency questionnaires.²⁰

Four cohort studies^{172,174,175,178} examining the effect of vitamin B-12 on AD incidence were eligible for inclusion. The studies included a total of 3192 subjects and identified an aggregate of 483 cases of AD over a period of follow-up ranging from three to 6.1 years. All four studies failed to detect a statistically significant association between AD and low dietary intake or low serum concentrations of vitamin B12 (HR/OR/RRs presented in section b). Based on the available evidence, the reviewers concluded that vitamin B12 did not appear to be associated with AD.²⁰

d) Study: Lee et al.⁶⁴

Year: 2010

AMSTAR score: 4

The review by Lee et al. examined the association between a number of lifestyle-related risk factors and AD.⁶⁴ One¹⁷² of the included studies examined the association between vitamin B-12 intake and risk of AD. The study included 816 subjects, 70 of which developed AD over an average of 3.8 years of follow-up. The exposure was ascertained according to serum nutrient levels. The method employed for outcome ascertainment was not specified in the review. There was no significant association between serum concentrations of vitamin B-12 and risk of AD according to the study (HR presented in section b). The reviewers concluded that “nutrients, such as...vitamin B12, were not shown to be protective.”⁶⁴

Table 5 – Vitamin B-12 and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies^a	Results	Conclusion
Raman et al. ¹⁶⁹ (2007)	Amstar Score: 5 Publication Bias Assessed: No	To examine the effect of vitamin B-6, vitamin B-12, and folate on AD and other cognitive outcomes.	1966 to November 2006	1. Medline 2. Commonwealth Agricultural Bureau Abstracts	9	4 of 7	1. Serum/plasma concentrations: Seven studies examining the effect of vitamin B-12 blood concentrations failed to detect an association with AD. One detected an increased risk of AD associated with low vitamin B 12 concentration. 2. Dietary intake: The only study to report on dietary intake also failed to detect an association.	Vitamin B-12 was not associated with AD
Dangour et al. ¹⁴⁴ (2010)	Amstar score: 5 Publication Bias Assessed: No	To examine the effect of B-vitamins and other dietary exposures on risk of AD	Not specified. Databases accessed on July 2007.	1. PubMed 2. Embase 3. Cochrane Library	7	Referent	1. Serum/plasma concentrations: All four studies failed to detect an association. 2. Dietary intake: All three studies failed to detect an association.	Available evidence was inconclusive regarding association between AD and B-vitamins.

Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of vitamin B12	To examine the effect of several factors, including vitamin B-12, on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	4	4 of 7	All four primary studies failed to detect an association.	Vitamin B-12 was not associated with risk of AD.
Lee et al. ⁶⁴ (2010)	Amstar Score: 4 Publication Bias Assessed: No	To examine the effect of several factors on the risk of developing AD and other cognitive outcomes.	All years up to August 2008	1. Pubmed 2. Embase 3. PsychInfo	1	1 of 7	The only identified study failed to detect an association.	Vitamin B-12 did not appear to reduce risk of AD.

^a"Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent". Item adopted from White, CM et al.⁵¹

3.6.2 Vitamin B-6

a) Study: Raman et al.¹⁶⁹

Year: 2007

AMSTAR score: 5

The effect of B-vitamins and risk of AD was examined by Raman et al.¹⁶⁹ Inclusion was restricted to cohort and case-control studies which adequately distinguished between AD and all-cause dementia. The review included two cohort studies^{173,175} which observed an aggregate of 244 cases of AD (N=2133) over a period of follow-up ranging from 3.9 to eight years. Two case-control studies^{165,179}, which examined a total of 107 cases and 101 controls, were also eligible for inclusion.

Two studies^{173,179} reported on the effect of blood concentrations of vitamin B-6. Both failed to detect an association (OR/RRs not reported in review). With respect to dietary intake, one case-control study¹⁶⁵ detected an association between low intake of vitamin B6 and AD (OR not reported in review). One cohort study¹⁷⁵ failed to detect an association between low intake and development of AD. The reviewers concluded that the available evidence was not suggestive of an association between vitamin B-6 and AD.¹⁶⁹

b) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Health Technology Assessment (HTA) prepared for the US Agency for Healthcare Research and Quality examined the effect of vitamin B-6 on incident AD.²⁰ Outcome ascertainment was achieved according to DSM or NINCDS-ADRDA criteria. The exposure was ascertained according to food frequency questionnaires.²⁰ Two cohort studies, which observed an aggregate of 353 cases of AD (N=2006) over a duration of follow-up ranging from 3.9 to 6.1 years, were included.

Vitamin B6 was not associated with AD according to both^{175,178} studies (*Total B6*¹⁷⁵ – OR: 0.70; 95% CI: 0.20, 2.40. *B6 from food*¹⁷⁵ – OR: 0.70; 95% CI: 0.30, 1.40. *Total B6 intake*¹⁷⁸ – No association; HR not reported). Based on the available evidence, the reviewers concluded that vitamin B-6 was not associated with risk of AD.²⁰

c) Study: Dangour et al.¹⁴⁴

Year: 2010

AMSTAR score: 5

The systematic review by Dangour et al. examined the association between several nutrients, including vitamin B-6, and risk of AD.¹⁴⁴ Included studies employed the DSM-III, DSM-IV, ICD-10, and NINCDS-ADRDA criteria for outcome ascertainment. Exposure status was ascertained according to serum or plasma nutrient levels, food diaries, and food frequency questionnaires.¹⁴⁴ Heterogeneity across the included studies precluded a meta-analysis.¹⁴⁴ Four relevant studies, which observed an aggregate of 493 cases (N=3677) over a period of follow-up ranging from 3.9 to 9.3 years, were included.

Of the four included cohort studies reporting on the association between vitamin B-6 and AD, two studies^{175,178} failed to detect an association between dietary intake of vitamin B-6 and risk of AD and one study¹⁷³ failed to detect an association between plasma vitamin B-6 levels and risk of AD (OR for one study¹⁷⁵ reported in section b. *>4.5 versus <2.3 mg/day*¹⁷⁸ – HR: 1.30; 95% CI: 0.70, 2.30). The remaining study¹⁷⁷ reported a reduced risk of AD associated with high vitamin B-6 consumption (*>reference daily allowance versus < reference daily allowance* – RR: 0.41; 95% CI: 0.20, 0.84). The reviewers concluded that the association between B-vitamins and AD was inconclusive.¹⁴⁴

Table 6 – Vitamin B-6 and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies^a	Results	Conclusion
Raman et al. ¹⁶⁹ (2007)	Amstar Score: 5 Publication Bias Assessed: No	To examine the effect of vitamin B-6, vitamin B-12, and folate on AD and other cognitive outcomes.	1966 to November 2006	1. Medline 2. Commonwealth Agricultural Bureau Abstracts	4	2 of 4	1. Serum/plasma concentrations: Both studies failed to detect an association. 2. Dietary intake: One study detected an association between low vitamin B-6 and risk of AD while the other reported null findings.	Vitamin B6 was not associated with AD.
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of vitamin B6	To examine the effect of several factors, including vitamin B-6, on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	2	2 of 4	Both cohort studies failed to detect an association.	Vitamin B-6 was not associated with risk of AD.
Dangour et al. ¹⁴⁴	Amstar score: 5 Publication	To examine the effect of B-vitamins	Not specified. Databases	1. PubMed 2. Embase 3. Cochrane	4	Referent	1. Serum/plasma concentrations: Both studies failed to detect	Association was inconclusive.

(2010)	Bias Assessed: No	and other dietary exposures on risk of AD	accessed on July 2007.	Library			an association. 2. Dietary intake: One study reported a protective effect associated with high vitamin B-6 consumption (RR: 0.41; 95% CI: 0.20, 0.84). The other failed to detect an association.	

^aNumber of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent". Item adopted from *White, CM et al.*⁵¹

3.6.3 Vitamin B3/Niacin

a) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Health Technology Assessment (HTA) prepared for the US Agency for Healthcare Research and Quality examined the effect of vitamin B-3, also known as niacin.²⁰ Outcome ascertainment was achieved according to DSM or NINCDS-ADRDA criteria.²⁰ The exposure was ascertained according to food frequency questionnaires.²⁰

A single cohort study¹⁸⁰, which observed 131 cases of AD (N=815) over an average of 3.9 years of follow-up, was included. The highest quintile of total niacin/vitamin B3 intake was associated with a reduced risk of AD (OR: 0.20; 95% CI: 0.01, 0.70). In the same study, tryptophan (“niacin dietary precursor”) (OR: 0.40; 95% CI: 0.10, 0.80), niacin obtained from food (OR: 0.30; 95% CI: 0.10, 0.70), and “niacin equivalents” (OR: 0.20; 95% CI: 0.10, 0.80) were all associated with a statistically significant reduced risk of AD.

b) Study: Lee et al.⁶⁴

Year: 2010

AMSTAR score: 4

The review by Lee et al. examined the association between a number of lifestyle-related risk factors and AD.⁶⁴ The reviewers captured the same study¹⁸⁰ included by Williams et al.²⁰ Based on the results of this single study, the reviewers concluded that niacin appeared to “show a protective effect”.⁶⁴

Table 7 – Vitamin B-3/Niacin and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies ^a	Results	Conclusion
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of vitamin B3	To examine the effect of several factors, including vitamin B-6, on the risk of developing AD.	1984- October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	1	Referent	Only identified cohort study reported a reduced risk of AD associated with high niacin intake (OR: 0.20; 95% CI: 0.01, 0.70). Same study reported: niacin obtained from food (OR: 0.30; 95% CI: 0.10, 0.70); “niacin equivalents” (OR: 0.20; 95% CI: 0.10, 0.80)	Inadequate evidence. Further research required.
Lee et al. ⁶⁴ (2010)	Amstar Score: 4 Publication Bias Assessed: No	To examine the effect of several factors on the risk of developing AD and other cognitive outcomes.	All years up to August 2008	1. Pubmed 2. Embase 3. PsychInfo	1	1 of 1	Higher intake of niacin associated with protective effect (RR: 0.30; 95% CI: 0.10, 0.70) according to the only identified study	Niacin appeared to “show a protective effect”.

^aNumber of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent”. Item adopted from *White et al.*⁵¹

3.6.4 Vitamins C and E

a) Study: Weih et al.⁶²

Year: 2007

AMSTAR score: 6

The effect of vitamins C and E on the incidence of AD was examined in the review by Weih et al.⁶² Dietary consumption was assessed by food frequency questionnaires across all included studies.⁶² Outcome ascertainment was consistently done according to the NINCDS-ADRDA criteria. A pooled analysis of the identified evidence was not conducted.

Three cohort studies^{181,182,183} examined the effect of vitamin C, vitamin E or the combined effect of these vitamins on the risk of AD. The studies observed 324 cases of AD (N = 9595) during periods of follow-up ranging from three to six years. One of two studies reported an association between vitamin C alone and risk of AD (*Highest quintile*¹⁸² - RR: 1.03; 95% CI: 0.41, 2.56. *Per 1 SD increase*¹⁸¹ - RR: 0.82; 95% CI: 0.68, 0.99).

Two cohort studies reported a statistically or marginally significant reduced risk of AD associated with dietary vitamin E (*Highest quintile*¹⁸² - RR: 0.30; 95% CI: 0.10, 0.92. *Per SD increase*¹⁸¹ - RR: 0.82; 95% CI: 0.66, 1.00). Finally, one study¹⁸³ examined the combined effect of vitamin C and E intake. The study reported no association with risk of AD (RR: 1.81; 95% CI: 0.91, 3.63). The reviewers concluded that the effect of vitamins C and E on AD was unclear.

b) Study: Patterson et al.⁶³

Year: 2007

AMSTAR score: 4

The systematic review conducted by Patterson et al. examined the effect of several putative risk factors on the development of AD and other cognitive outcomes including unspecified dementia and vascular dementia.⁶³ One¹⁸⁴ identified study examined the effect of low serum vitamin E on AD risk. The nested case-control study included 46 dementia cases (39 with AD) and 136 controls. The

lowest tertile of serum vitamin E was not significantly associated with an increased risk of AD (RR: 2.10; 95 % CI: 0.81, 5.54).⁶³ No conclusions were drawn by reviewers regarding the effect of vitamin E.

c) Study: Lee et al.⁶⁴

Year: 2010

AMSTAR score: 4

The review by Lee et al. examined the effect of vitamins C and E on the risk of AD.⁶⁴ Methods for exposure and outcome ascertainment employed in the primary studies were not specified in the review. Heterogeneity across the included studies precluded a meta-analysis. The review identified four prospective cohort studies examining the risk of AD associated with vitamin C and E intake. The studies observed 553 cases of AD (N = 10423) during follow-up periods ranging from 4 to 33 years.

Three studies^{185,186,187} failed to detect an association between dietary intake of vitamin C and vitamin E and risk of AD (HR/RRs not reported). The remaining study¹⁸¹ reported a marginally significant reduced risk of AD associated with each standard deviation increase in vitamin C and E consumption (*Vitamin C* - RR: 0.82; 95% CI: 0.68, 0.99. *Vitamin E* - RR: 0.82; 95% CI: 0.66, 1.00). Based on these limited findings, the reviewers concluded that vitamin E may reduce risk of AD.⁶⁴ Reviewers concluded that the evidence was not suggestive of an association between vitamin C and AD.

d) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Health Technology Assessment (HTA), prepared for the US Agency for Healthcare Research and Quality, examined the effect of medical, social/behavioural, environmental, dietary, and pharmacological factors on the risk of AD.²⁰ Eleven studies examining the effect of vitamins C

and E were identified and included in the report. The studies observed an aggregate of 1514 cases of AD (N = 22414) during periods of follow-up ranging from 2.7 to 33 years. Outcome ascertainment was achieved according to DSM or NINCDS-ADRDA criteria across all studies.

Seven studies^{182,183,188,189,190,191,192} examined supplemental vitamin C and E intake, four studies^{181,182,186,193} examined dietary intake, and one study¹⁸⁷ examined both supplemental and dietary intake of vitamin C and E. Exposure status was ascertained through surveys¹⁸³, semi-quantitative food frequency questionnaires¹⁸⁷, and interviews¹⁸⁹ in three of the seven studies that examined supplemental intake. Three^{190,191,192} studies confirmed self-reported supplement intake using information obtained from medication bottles while one study¹⁸⁸ solely relied on information obtained from medication bottles for exposure ascertainment. Among the five studies that reported on vitamins C and E obtained from dietary sources, exposure status was ascertained according to food frequency questionnaires^{181,182,187,193} and 24-hour dietary recall¹⁸⁶.

Six of the included studies failed to detect a statistically significant association between dietary or supplemental intake of vitamins C and/or E and risk of AD (Vitamin C: *Masaki et al.*¹⁸³ – OR: 1.61; 95% CI: 0.67, 3.87. *Luchsinger et al.*¹⁸⁷ –RR not reported. *Fillenbaum et al.*¹⁸⁸ –RR not reported. *Gray et al.*¹⁸⁹ – HR: 0.95; 95% CI: 0.72, 1.25. *Maxwell et al.*¹⁹⁰ –RR not reported. Vitamin E: *Masaki et al.*¹⁸³ – OR: 0.84; 95% CI: 0.19, 3.77. *Luchsinger et al.*¹⁸⁷ –RR not reported. *Fillenbaum et al.*¹⁸⁸ –RR not reported. *Gray et al.*¹⁸⁹ – HR: 1.04; 95% CI: 0.78, 1.39. *Maxwell et al.*¹⁹⁰ –RR not reported. *Morris et al.*¹⁹¹ – p = 0.23. Vitamin C and E combined: OR for one study¹⁸³ reported in section a. *Fillenbaum et al.*¹⁸⁸ –RR not reported. *Gray et al.*¹⁸⁹ – HR not reported. *Maxwell et al.*¹⁹⁰ – OR: 1.00; 95% CI: 0.53, 1.87).

Four studies^{181,182,191,193} reported a marginally or statistically significant reduced risk of AD associated with higher intake of vitamin C or vitamin E (Vitamin C: RR for one study¹⁸¹ presented in section a. *Morris et al.*¹⁹¹ – p = 0.04. Vitamin E: RR for two studies^{181,182} presented in section a. *Morris et al.*¹⁹³ – RR: 0.74; 95% CI: 0.62, 0.88). One study reported an increased risk of AD associated with the second and fourth quartile of vitamin E intake (*Second quartile* – RR: 1.92; 95% CI: 1.16, 3.18. *Fourth quartile*¹⁸⁶ – HR: 1.78; 95% CI: 1.06, 2.98). Finally, one study¹⁹² examined the effect of combined supplementation of vitamin C and E. The study reported a marginally significant association with AD (HR: 0.36; 95% CI: 0.09, 0.99).

The reviewers concluded that there was insufficient evidence to suggest that vitamins C and E were associated with risk of AD.²⁰

Table 8 – Vitamins C and E and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies^a	Results	Conclusion
Weih et al. ⁶² (2007)	Amstar Score: 6 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD.	January 1966 to June 2006	1. Medline 2. Embase 3. Cochrane Database 4. Current Contents	3	3 of 11	1. Vitamin C: One of two studies detected a marginally significant reduced risk of AD associated with increasing vitamin C consumption (RR: 0.82; 95% CI: 0.68, 0.99). 2. Vitamin E: Both cohort studies reporting on vitamin E detected a reduced risk of AD associated with increasing vitamin E intake. Vitamin E not beneficial for delaying progression from MCI to AD according to one RCT. 3. Combined vitamin C and E: The only study to report on the effect of combined intake failed to detect an association (RR: 1.81; 95% CI: 0.91, 3.63)	Association with AD unclear.

Patterson et al. ⁶³ (2007)	Amstar Score: 4 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD and other cognitive outcomes.	1966 to December 2005	1. Medline 2. Embase	1	0 of 11	The only identified study failed to detect an association between vitamin E and risk of AD (RR: 2.10; 95 % CI: 0.81, 5.54).	No conclusions drawn by authors.
Lee et al. ⁶⁴ (2010)	Amstar Score: 4 Publication Bias Assessed: No	To examine the effect of several factors on the risk of developing AD and other cognitive outcomes.	All years up to August 2008	1. Pubmed 2. Embase 3. PsychInfo	4	3 of 11	Three of four identified studies failed to detect an association between vitamin C or E and risk of AD. One study reported a marginally significant reduced risk of AD associated with increasing vitamin C(RR: 0.82; 95% CI: 0.68, 0.99) and E (RR: 0.82; 95% CI: 0.66, 1.00)	Vitamin E may reduce risk of AD. No association between vitamin C and AD.
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of vitamins C/E	To examine the effect of several factors, including vitamin C/E, on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	11	Referent	Six studies failed to detect an association between vitamin C and/or vitamin E and risk of AD. Four studies reported a reduced risk of AD associated with high intake of vitamins C or E. One study reported an increased risk of AD with increasing intake of vitamin E. One study detected a protective effect of combined supplementation of vitamins C and E.	Inadequate evidence to suggest an association between vitamins C and E and risk of incident AD.

^a"Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent". Item adopted from White et al.⁵¹

3.6.5 Multivitamins

a) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Health Technology Assessment (HTA), prepared for the US Agency for Healthcare Research and Quality, reviewed the effect of supplemental multivitamin use on the risk of incident AD.²⁰ Two^{189,192} cohort studies were identified. Exposure status was ascertained according to self-reported use in both studies. One study confirmed self-reported supplement intake using information obtained from medication bottles.¹⁹² Alzheimer's disease was diagnosed according to the NINCDS-ADRDA and DSM criteria. Two cohort studies, which observed an aggregate of 393 cases (N=6196) over follow-up periods ranging from three to 5.5 years, were included.

According to the results of both cohort studies, multivitamin use was not significantly associated with a reduced risk of AD (*Gray et al.*¹⁸⁹ - HR: 0.94; 95% CI: 0.72, 1.22. *Zandi et al.*¹⁹² – HR not reported).

Table 9 – Multivitamin use and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Results	Conclusion
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of multivitamins	To examine the effect of several factors, including multivitamins, on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	Both identified studies failed to detect an association.	No conclusions drawn by authors.

3.6.6 Flavanoids

a) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Health Technology Assessment (HTA), prepared for the US Agency for Healthcare Research and Quality, identified three cohort studies^{181,186,194} that reported on the association between flavonoid intake and risk of AD. The studies observed an aggregate of 294 cases of AD (N=9221) during periods of follow-up ranging from two to 33 years. Exposure status was ascertained according to semi-quantitative food frequency questionnaires¹⁸¹, 24-hour dietary recall¹⁸⁶, and combined methods¹⁹⁴ including self- and dietician-administered questionnaires.²⁰ The outcome was consistently diagnosed according to NINCDS-ADRDA and DSM criteria across all three studies.²⁰

Dietary flavonoid intake was analyzed categorically in two studies^{186,194}. Only one of the two studies reported a statistically significant association between flavonoid intake and risk of AD. However, the study¹⁹⁴ reported a reduced risk associated with moderate but not high intake (*Moderate* - HR: 0.45; 95% CI: 0.22, 0.92. *High* –HR not reported). When the high and moderate tertile categories were collapsed and compared to the lowest tertile of intake, higher consumption of dietary flavonoids was associated with a statistically significant reduced risk of AD (HR: 0.49; 95% CI: 0.26, 0.92).²⁰ The third study¹⁸¹ reported no association between increasing flavonoid intake and AD (*Per SD increase* - HR: 0.99; 95% CI: 0.83, 1.18).²⁰ The reviewers concluded that the evidence was suggestive of a lack of association between flavonoid intake and risk of AD.

b) Study: Lee et al.⁶⁴

Year: 2010

AMSTAR score: 4

The systematic review by Lee et al.⁶⁴ examined the association between AD and a number of dietary factors including flavonoids. Two^{181,186} of the three studies identified in the HTA²⁰ were also

identified by Lee et al. The studies observed 248 cases of AD (N=7854) over periods of follow-up ranging from six to 33 years. Both cohort studies failed to detect a statistically significant association between dietary flavonoid consumption and risk of AD. Findings of this review suggest that dietary flavonoids do not protect against the risk of AD.⁶⁴

Table 10 – Flavonoids and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies ^a	Results	Conclusion
Lee et al. ⁶⁴ (2010)	Amstar Score: 4 Publication Bias Assessed: No	To examine the effect of several factors on the risk of developing AD and other cognitive outcomes.	All years up to August 2008	1. Pubmed 2. Embase 3. PsychInfo	2	2 of 3	Both identified studies failed to detect an association.	Flavonoids do not exert a protective effect against the development of AD.
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of flavonoids	To examine the effect of several factors, including vitamin B-6, on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	3	Referent	Two of three studies failed to detect an association between flavonoid consumption and risk of AD. One study detected a protective effect associated with higher tertiles of flavonoid consumption (HR: 0.49; 95% CI: 0.26, 0.92).	Flavonoids do not exert a protective effect against the development of AD.

^aNumber of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent⁵¹. Item adopted from *White et al.*

3.6.7 Beta-carotene

a) Study: Weih et al.⁶²

Year: 2007

AMSTAR score: 6

One cohort study¹⁸² identified in the systematic review by Weih et al.⁶² examined the association between beta-carotene intake and risk of AD. The study included 815 subjects, 131 of which developed AD over an average of 3.9 years of follow-up. Beta-carotene intake was ascertained using a semi-quantitative food frequency questionnaire.⁶² AD was diagnosed according to the NINCDS-ADRDA criteria. According to the results of the study, low beta-carotene consumption was not associated with AD (RR: 0.55; 95% CI: 0.22, 1.35).⁶²

b) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Health Technology Assessment (HTA) identified four community cohort studies which examined the effect of carotenoids or beta-carotene on the risk of AD. Four cohort studies, which observed 621 cases of AD (N = 9649) over periods of follow-up ranging from 3.9 to 33 years, were included. Exposure status was ascertained according to food frequency questionnaires^{181,182,187} and 24-hour dietary recall¹⁸⁶. AD was diagnosed according to NINCDS-ADRDA and DSM criteria.²⁰

All four studies failed to detect an association between beta-carotene and risk of AD (RRs not reported for three studies^{182,186,187}. *Engelhart et al.*¹⁸¹ - HR: 0.87; 95% CI: 0.70, 1.09). The reviews concluded that beta-carotene intake was not associated with AD.²⁰

c) Study: Lee et al.⁶⁴

Year: 2010

AMSTAR score: 4

The systematic review by Lee et al.⁶⁴ identified four cohort studies^{181,185,186,187} which examined the effect of beta-carotene and other carotenoids on the risk of AD. The studies observed an aggregate of 553 cases of AD (N = 10423) over periods of follow-up ranging from 4 to 33 years. Three^{181,186,187} of these studies were also identified in the review reported by Williams et al.²⁰ Methods employed for exposure and outcome ascertainment were not specified in the review. All four studies failed to detect an association between beta-carotene/carotenoids and AD (HR/RRs not reported in review for all four studies).⁶⁴

Table 11 – Beta-carotene and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies^a	Results	Conclusion
Weih et al. ⁶² (2007)	Amstar Score: 6 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD.	January 1966 to June 2006	1. Medline 2. Embase 3. Cochrane Database 4. Current Contents	1	1 of 4	The only identified study failed to detect an association.	Beta-carotenes did not appear to exert a protective effect according to the only identified study.
Lee et al. ⁶⁴ (2010)	Amstar Score: 4 Publication Bias Assessed: No	To examine the effect of several factors on the risk of developing AD and other cognitive outcomes.	All years up to August 2008	1. Pubmed 2. Embase 3. PsychInfo	4	3 of 4	All four studies failed to detect an association.	No evidence to support an association between beta-carotene consumption and risk of AD.
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of beta-carotenes	To examine the effect of several factors on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	4	Referent	All four studies failed to detect an association.	Beta-carotenes were not associated with AD.

^a“Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent”. Item adopted from *White et al.*⁵¹

Discussion

Considered cumulatively, none of the examined micronutrients showed a consistent association with AD. However, the small number of primary studies precluded a definitive conclusion for a majority of micronutrients. In general, the identified systematic reviews yielded consistent conclusions. This is attributed to the considerable primary study overlap across reviews reporting on the same micronutrients. The extent of overlap is summarized in the risk factor-specific evidence tables (Tables 5 to 11).

For the most part, primary studies examining the effect of micronutrients yielded inconsistent findings. Discordant results across primary studies are possibly attributed to the lack of consistent thresholds delineating exposure status.²⁰ Further studies, which rely on standardized exposure thresholds, are required. Limitations pertaining to exposure ascertainment must also be noted. Studies examining the effect of micronutrient intake relied on subjective measurement tools, namely, food frequency questionnaires and 24-hour dietary recall.²⁰ Exposure measurement tools reliant on self-reported dietary intake are often affected by perceptions of health which may lead to exposure measurement error. Also, FFQs are likely to underestimate the true association.¹⁵⁷

Failure to detect an association between AD and isolated micronutrients is believed to be attributed to the concept of food synergy.¹⁹⁵ That is, nutrients are likely to affect health outcomes in combination rather than individually through numerous and complex biological mechanisms.¹⁹⁵ The study of isolated micronutrients disregards the synergistic effects afforded by foods or dietary patterns.¹⁹⁵ However, studies that examined the combined effect of micronutrients have also failed to detect an association with AD or have yielded discordant findings. For example, studies reporting on the combined effect of vitamins C and E were inconsistent. Further, a systematic review²⁰ examining the effect of multivitamins, which include several micronutrients, identified two primary studies yielding null findings. These results may suggest that micronutrients may not affect disease risk. Future studies should rely on objective measures for exposure ascertainment, use standardized exposure thresholds, and consider the effect of micronutrients in combination.

3.7 Fruits and Vegetables

The putative association between fruit and vegetable consumption and risk of AD is attributed to their antioxidant properties.¹⁹⁶ Two^{20,64} moderate-quality systematic reviews examined the effect of fruit and vegetable intake and risk of subsequent risk of incident AD. Findings from these reviews are summarized below.

a) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

Two^{185,196} cohort studies, which examined the effect of fruit and vegetable intake on AD risk, were eligible for inclusion in the HTA²⁰. Exposure status was ascertained according to self-report and AD was diagnosed according to NINCDS-ADRDA and DSM criteria.²⁰ The studies examined an aggregate of 5368 subjects, 303 of which were diagnosed with AD. Duration of follow-up ranged from 6.3 to 31.5 years.

Both included studies reported a reduced risk of AD associated with fruit and vegetable consumption. One study¹⁸⁵ reported that consumption of fruit and vegetable juice three or more times per week was associated with a reduced risk of AD (HR: 0.24; 95% CI: 0.09, 0.61). Moderate or high intake of fruits and vegetables in midlife was also associated with a reduced risk of AD according to the second study¹⁹⁶ (OR: 0.60; 95% CI: 0.41, 0.86). However, stratified analysis revealed that the association was statistically significant for women (OR: 0.47; 95% CI: 0.31, 0.73) and among those with angina (OR: 0.32; 95% CI: 0.16, 0.65), only.

Based on the available evidence, the reviewers conclude that high consumption of fruits and vegetables appeared to be associated with a reduced risk of AD.²⁰ However, these findings were limited by the small number of available of studies.

d) Study: Lee et al.⁶⁴

Year: 2010

AMSTAR score: 4

Lee et al.⁶⁴ identified one of the cohort studies¹⁸⁵ also captured in the review reported by Williams et al.²⁰

Discussion

The available evidence pertaining to the association between fruit and vegetable intake and risk of AD was scarce. Results of these reviews must be interpreted with caution due to the limited number of primary studies available for analysis and potential sources of bias attributed to exposure ascertainment. Both cohort studies relied on self-reported consumption which may increase susceptibility to exposure measurement error as evidence suggests that consumption of healthy foods are overreported.^{20,92}

Table 12 – Fruit and vegetable consumption and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies^a	Results	Conclusion
Lee et al. ⁶⁴ (2010)	Amstar Score: 4 Publication Bias Assessed: No	To examine the effect of several factors on the risk of developing AD and other cognitive outcomes.	All years up to August 2008	1. Pubmed 2. Embase 3. PsychInfo	1	1 of 2	The only identified cohort study detected a protective effect associated with fruit and vegetable consumption three or more times per week (HR: 0.24; 95% CI: 0.09, 0.61)	No conclusions drawn by authors
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of fruit and vegetable intake	To examine the effect of several factors on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	2	Referent	Both prospective cohort studies detected an association between fruit and vegetable consumption and risk of AD.	Some evidence of an association. Further research required.

^a“Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent”. Item adopted from White et al.⁵¹

3.8 Caffeine

Research suggests that caffeine intake exerts a protective effect against the development of Parkinson's disease.¹⁹⁷ A similar neuroprotective effect of caffeine consumption against the development of AD has also been observed.¹⁹⁸ Two biological mechanisms have been presented regarding the putative protective role of caffeine against the development of AD. Firstly, an in vitro study found that caffeine, an adenosine receptor antagonist, protects against the development of AD by "[reversing] cognitive impairment and [decreasing] brain amyloid- β levels in aged AD mice".¹⁹⁹ Secondly, coffee, the most abundant source of caffeine, contains antioxidants which may mitigate the neurodegenerative effects of oxidative stress and vascular risk factors.^{198,199}

Three moderate quality systematic reviews^{64,197,198} examining the effect of caffeine consumption on the risk of AD were identified and included in the complex review. Meta-analyses were conducted in two^{197,198} of the three reviews. Findings from these reviews are qualitatively summarized.

a) Study: Barranco Quintana et al.¹⁹⁸

Year: 2007

AMSTAR score: 4

The systematic review and meta-analysis conducted by Barranco Quintana et al. examined the association between coffee consumption and risk of AD.¹⁹⁸ Studies were retrieved through a Medline and PscyLit database search.¹⁹⁸ Two case-control^{101,200}, one nested case-control⁷⁶, and one cohort²⁰¹ study were identified and eligible for inclusion in the review. The case-control studies included an aggregate of 224 cases and 224 controls. The nested case-control study included 194 cases of AD and 3894 controls. The cohort study included 694 subjects, 36 of which developed AD over five years of follow-up. Coffee consumption was ascertained via interview and self-administered questionnaires.¹⁹⁸ Statistical heterogeneity across included studies was examined according to the chi-square test and a random effects model was used to meta-analyze the data.¹⁹⁸

One nested case-control⁷⁶ and one case-control study²⁰⁰ reported a reduced risk of AD associated with coffee consumption. The remaining studies reported no association. The fixed

effects meta-analysis detected a reduced risk of AD associated with coffee consumption (Risk estimate: 0.73; 95% CI: 0.58, 0.92; Test for heterogeneity: $\chi^2 = 13.6$, $p < 0.01$). Presence of statistical heterogeneity necessitated the use of a random effects model. The random effects meta-analysis yielded non-significant findings (Risk estimate: 0.79; 95% CI: 0.46, 1.36). The computed pooled estimate is incorrect due to inappropriate pooling of studies as described in the discussion section (page 130).

To investigate potential sources of heterogeneity across the included studies, the reviewers conducted a series of sensitivity analyses.¹⁹⁸ The sensitivity analysis which included the nested case-control⁷⁶ and cohort study²⁰¹ suggested that coffee consumption was associated with a marginally significant decreased risk of AD (Risk estimate: 0.73; 95% CI: 0.54, 0.99). The pooled analysis restricted to the case-control studies^{101,200} failed to reach statistical significance (Risk estimate: 0.73; 95% CI: 0.50, 1.05). A pooled analysis of the three studies^{76,101,200} that employed interview questionnaires for exposure ascertainment yielded results suggesting a 30% reduced risk of AD associated with coffee consumption (Risk estimate: 0.70; 95% CI: 0.55, 0.90). Lastly, the reviewers conducted a subgroup analysis excluding the studies by Broe et al.¹⁰¹, which failed to adjust for potentially confounding variables, and Tyas et al.²⁰¹, which was susceptible to exposure measurement bias associated with the use of self-administered questionnaires.¹⁹⁸ Results were statistically significant (Risk estimate: 0.58; 95% CI: 0.44, 0.77).

According to the random effects meta-analysis, coffee consumption was not significantly associated with risk of AD.¹⁹⁸ However, sensitivity analyses restricted to cohort studies, studies employing interview questionnaires, and studies that were less susceptible to bias, all support the protective effect of coffee consumption against the development of AD.¹⁹⁸ The reviewers concluded that “coffee consumption [was] inversely associated with the risk of AD”.¹⁹⁸ However, the reviewers cautioned that results were limited by the small number of available studies and the presence of heterogeneity.

b) Study: Santos et al.¹⁹⁷

Year: 2010

AMSTAR score: 6

The systematic review and meta-analysis by Santos et al. examined the effect of caffeine consumption on the risk of dementia, AD, and cognitive impairment.¹⁹⁷ Studies were retrieved through an electronic database search which was supplemented with a bibliographic review of relevant studies.¹⁹⁷ Two case-control^{101,200}, one nested case-control⁷⁶, and two cohort^{201,202} studies reported on the association between caffeine intake and the risk of AD. The case-control studies included an aggregate of 224 cases and 224 controls. The cohort studies observed a total of 84 cases of AD (N = 2103) during periods of follow-up ranging from five to 21 years. The nested case-control study included 194 cases of AD and 3894 controls.

The exposure was ascertained according to interviewer^{101,201} and self-administered^{76,201} questionnaires in three studies. The remaining two studies^{200,202} also utilized questionnaires for exposure measurement; however, further detail regarding the data collection process was not specified. There was heterogeneity across the included studies pertaining to the type of caffeinated beverages under investigation and the categorization of the exposure.¹⁹⁷ The studies by Tyas et al.²⁰¹, Eskelinen et al.²⁰², and Lindsay et al.⁷⁶ provided risk estimates for coffee and tea intake separately, Broe et al.¹⁰¹ provided data pertaining solely to coffee consumption, and Maia et al.²⁰⁰ considered all caffeinated beverages.¹⁹⁷ Maia et al.²⁰⁰ and Broe et al.¹⁰¹ compared ever to never consumers¹⁹⁷. In contrast, the studies by Tyas et al.²⁰¹ and Lindsay et al.⁷⁶ compared regular (daily or "nearly every day") caffeine consumption to irregular consumption. Lastly, two studies^{101,202} provided data comparing the risk of AD associated with specific quantities of caffeine intake. The study by Broe et al.¹⁰¹ compared those consuming less than four cups of coffee a day to those consuming four or more cups a day. Similarly, the study by Eskelinen et al.²⁰² examined the effect of consuming zero to two cups of coffee compared to three to five cups. Eskelinen et al.²⁰² also reported the effect of heavy coffee consumption (more than 5 cups) compared to none or low coffee consumption (0 to 2 cups). AD was consistently diagnosed according to the NINCDS-ADRDA across all included studies.¹⁹⁷ A random effects model was employed to compute a pooled risk estimate.¹⁹⁷ Publication bias was examined according to visual inspection of the funnel plot, Begg's adjusted rank correlation test, and Egger's regression asymmetry test.¹⁹⁷

Among the five included studies, three^{101,201,202} failed to detect an association between coffee consumption and risk of AD. The remaining two studies^{76,200} reported a statistically significant decreased risk of AD among coffee consumers.¹⁹⁷ Three studies^{76,201,202} provided risk estimates restricted to tea intake. All three studies failed to detect a statistically significant association.

The reviewers conducted a pooled analysis. In the case that a study provided multiple risk estimates the "most precise measures of association" were used for the pooled analysis.¹⁹⁷ Moreover, the study by Eskelinen et al.²⁰² was excluded from the meta-analysis for AD as the risk estimate provided for "any dementia" was more precise.¹⁹⁷ Lastly, for studies reporting on the effect of tea and coffee consumption separately, only the measure of association for coffee consumption was included in the meta-analysis examining the effect of caffeine intake. Overall, four studies^{76,101,201,200} were eligible for inclusion in the meta-analysis. Results of the meta-analysis suggested that caffeine consumption was associated with a reduced risk of AD (RR: 0.62; 95% CI: 0.45, 0.87). The test for heterogeneity was not statistically significant ($p=0.169$; $I^2=40.5\%$).¹⁹⁷ Funnel plot inspection and results of statistical tests were suggestive of the absence of publication bias (Egger's regression asymmetry test: $p=0.277$; Begg adjusted rank correlation test: $p=0.784$).¹⁹⁷

The reviewers concluded that while there was evidence of a reduced risk of AD associated with caffeine consumption, results were limited by the presence of methodological heterogeneity.¹⁹⁷

c) Study: Lee et al.⁶⁴

Year: 2010

AMSTAR score: 4

The review by Lee et al. examined the association between a number of lifestyle-related risk factors and AD.⁶⁴ One¹⁸⁵ of the included studies examined the effect of tea consumption on the risk of AD. The study included 1589 subjects, 63 of which developed AD over an average of 6.3 years of follow-up. Methods employed for exposure and outcome ascertainment in the primary study were not specified in the review. Tea consumption was not associated with risk of AD according to the study (RR: not reported in review).

Discussion

Three moderate quality systematic reviews^{64,197,198} examined the association between coffee or caffeine intake and risk of AD. Among the six primary studies identified across the three reviews, only two^{76,200} studies reported a statistically significant association between caffeine consumption and risk of AD. Moreover, the most recent cohort study²⁰² with the longest length of follow-up also failed to detect an association.

Random effects meta-analyses were conducted in two of the included reviews. Although the random effects pooled analysis by Barranco Quintana et al.¹⁹⁸ failed to reach statistical significance, the random effects meta-analysis reported by Santos et al.¹⁹⁷, which considered the same four studies, found a statistically significant reduced risk of AD associated with caffeine consumption. The reviews varied with respect to how results from one primary study were incorporated into the meta-analysis. The primary study¹⁰¹ in question reported risk of AD associated with “never consumption” of coffee (OR: 1.55; 95% CI: 0.89, 2.71). Using data from the primary study, Santos et al. “computed the OR using non-consumers as the reference class” and relied on this estimate for the meta-analysis (OR: 0.65; 95% CI: 0.36, 1.19).¹⁹⁷ In contrast, Barranco Quintana et al.¹⁹⁸ relied on the reported risk estimate which used *consumers* as the referent category (OR: 1.55; 95% CI: 0.89, 2.71). Because the remaining three studies included in the meta-analyses presented risk estimates using non-consumers as the referent category, Barranco Quintana et al.¹⁹⁸ should have computed the risk estimate using non-consumers as the referent category to allow for appropriate pooling. As a result of this discrepancy, the quantitative analyses yielded conflicting results.

The included reviews are limited by the small number of available studies and heterogeneity across the studies with respect to the type and quantity of caffeinated beverages under investigation.^{197,198} Conclusions drawn from the systematic reviews are also limited by methodological limitations of the included observational studies. Case-control studies, in particular, are susceptible to recall bias.⁷¹ Case-control studies of cognitively impaired subjects face the added challenge of ascertaining exposure status of cognitively impaired or demented cases who often lack the capacity to recall past exposures.²¹ Consequently, a proxy respondent is often recruited to provide data for the purpose of exposure ascertainment.²¹ The susceptibility for recall bias is further heightened if methods for exposure ascertainment are not parallel across outcome categories.⁷² In the case-control study by Maia et al.²⁰⁰, for example, the exposure status of controls was ascertained according to self-report while proxy respondents were recruited to ascertain the exposure status of

cases. If we assume that there is an increased likelihood of exposure recall error among cases, as data was obtained from an informant rather than from the subject directly, the association between caffeine intake and risk of AD is likely attenuated.^{71,72} Both case-control and cohort studies, however, are susceptible to exposure measurement error arising from the use of subjective tools, namely, interview- or self-administered questionnaires. Such subjective methods may lead to exposure measurement error, since self-reported dietary intake is often affected by perceptions of health.⁹² More specifically, studies have found that unhealthy foods are often underreported while consumption of healthy foods are overreported.⁹² Although less practical, use of objective measurement tools, such as urinary biomarkers, would provide a more accurate measure of coffee consumption and ultimately improve the validity of study findings.^{203,204}

Caffeine consumption is associated with health and lifestyle factors which can potentially confound the association between caffeine intake and AD risk, namely smoking and alcohol consumption.¹⁹⁸ Only two^{200,202} of the six observational studies included in the three systematic reviews adjusted for lifestyle related risk factors for AD.

Overall, based on the conflicting findings of the observational studies, the association between coffee or caffeine consumption and risk of AD was inconclusive. Further research investigating the effect of caffeine consumption on the risk of AD is required.^{197,198}

Table 13 – Coffee/Caffeine consumption and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies^a	Results	Conclusion
Barranco Quintana et al. ¹⁹⁸ (2007)	Amstar score: 4 Publication Bias Assessed: No	To investigate the association between coffee consumption and Alzheimer's disease.	All years from the inception of the databases to January 2004	1. Medline 2. Current Contents Best Evidence 3. Nisc Mexico Biblioline	4	4 of 5	1. Coffee consumption vs. Nonconsumption: (Risk estimate: 0.79; 95% CI: 0.46, 1.36) 2. Cohort studies: (Risk estimate: 0.73; 95% CI: 0.54, 0.99) 3. Case-control studies: (Risk estimate 0.73; 95% CI: 0.50, 1.05) 4. Studies using interview questionnaires: (Risk estimate: 0.70; 95% CI: 0.55, 0.90) 5. Excluding studies susceptible to bias:	Overall pooled analysis failed to detect an association; however, subgroup analyses detected a reduced risk attributed to caffeine consumption.

							(Risk estimate: 0.58; 95% CI: 0.44, 0.77)	
Santos et al. ¹⁹⁷ (2010)	Amstar score: 6 Publication Bias Assessed: Yes	To examine the association between caffeine and Alzheimer's disease, dementia, and cognitive decline.	All years from inception of the databases to September 2009	1. Medline 2. LILACS (Latin America and Caribbean) 3. Scopus 4. Web of Science	5	Referent	1. Ever vs. Never: (RR: 0.62; 95% CI: 0.45, 0.87; Test for statistical heterogeneity: $I^2 = 40.5\%$)	Caffeine consumption appeared to decrease risk of AD.
Lee et al. ⁶⁴ (2010)	Amstar Score: 4 Publication Bias Assessed: No	To examine the effect of several factors on the risk of developing AD and other cognitive outcomes.	All years up to August 2008	1. Pubmed 2. Embase 3. PsychInfo	1	0 of 5	The only identified study failed to detect an association between tea consumption and risk of AD.	No conclusions drawn by reviewers.

^a "Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent". Item adopted from White et al.⁵¹

3.9 Mediterranean diet

Research suggests that adherence to the Mediterranean dietary pattern is protective against mortality and the development of cardiovascular and neurodegenerative conditions.²⁰⁹ This dietary pattern is comprised of a number of components including: (1) high intake of legumes, cereals, fruits, vegetables, and fish, (2) low intake of meat and dairy products, (3) moderate intake of alcohol, and (4) a high mono-unsaturated fatty acid to saturated fatty acid ratio.²⁰⁸ It is hypothesized that the cardiovascular risk reduction afforded by this dietary pattern may in turn protect against the development of AD.²⁰⁵ Moreover, high levels of antioxidants and vitamins obtained from the Mediterranean diet may mitigate the effects of inflammation and oxidative stress, factors likely involved in the etiology of AD.²⁰⁵

Six systematic reviews^{20,60,62,206,209,208} examined the association between adherence to the Mediterranean diet and risk of AD. Two reviews^{60,206} were of poor methodological quality according to the AMSTAR criteria and were consequently excluded. Of the remaining studies, three were of moderate methodological quality^{20,62,208} and one was a high quality review²⁰⁹. Findings from these reviews are qualitatively summarized.

a) Study: Weih et al.⁶²

Year: 2007

AMSTAR score: 6

The effect of adherence to the Mediterranean diet was examined in the review by Weih et al.⁶² Only one study²⁰⁷ was identified. The study examined 2258 subjects, 262 of which developed AD over four years of follow-up. Adherence was assessed by a semi quantitative food frequency questionnaire and outcome ascertainment was achieved according to acceptable criteria.⁶² According to the results of the cohort study, the highest tertile of Mediterranean diet adherence was associated with a decreased risk of incident AD (HR: 0.60; 95% CI: 0.40, 0.90). Although only a single cohort study was identified, the reviewers concluded that there was “good evidence...that Mediterranean diet...might be protective”.⁶²

b) Study: Sofi et al.²⁰⁸

Year: 2008

AMSTAR score: 6

The systematic review by Sofi et al. examined the effect of the Mediterranean dietary pattern on the risk of numerous outcomes including Alzheimer's disease, Parkinson's disease, cancer, and mortality.²⁰⁸ Studies were identified through a search of PubMed, Embase, Web of Science, and Cochrane Central.²⁰⁸ Inclusion was restricted to prospective cohort studies that ascertained adherence to the diet according to a scoring system.²⁰⁸ Only one²⁰⁷ of the included studies, however, focused on the risk of AD. This study was also captured in an earlier review reported by Weih et al.⁶² Adherence to the Mediterranean diet was quantified according to a scoring system in the cohort study. Adherence to each food group of the Mediterranean diet was examined. Those consuming quantities exceeding the population median were assigned a score of one while those consuming quantities less than the established threshold were assigned a score of zero.²⁰⁸ Conversely, those with a high intake of foods atypical of the Mediterranean diet, such as meats and dairy, were assigned a score of zero.²⁰⁸ Those with a low intake (below the population median) of these food groups were given a score of one.²⁰⁸ A single combined score was derived with a total score ranging from 7 to 9 indicating high adherence to the Mediterranean diet.²⁰⁸ The criteria employed for outcome ascertainment in the primary study was not specified in the systematic review. A meta-analysis examining the effect of the Mediterranean diet on the incidence of neurological conditions (AD and Parkinson's disease) was conducted. Because the results of the meta-analysis were not specific to the outcome of AD, findings of the quantitative analysis will not be presented. Finally, publication bias was examined according to the fail safe N method.²⁰⁸

The reviewers converted the results from all primary studies to examine the effect of a two-point increased risk in adherence score.²⁰⁸ The primary study reported by Scarmeas et al.²⁰⁷ detected a reduced risk of AD associated with each two-point increase in Mediterranean diet adherence score (RR: 0.83; CI 0.70, 0.98). There was no evidence of publication bias. Conclusions were drawn for the effect of Mediterranean diet adherence on the incidence of Parkinson's disease and AD combined. However, conclusions were not drawn for AD considered separately.

c) Study: Sofi et al.²⁰⁹

Year: 2010

AMSTAR score: 9

The 2010 systematic review by Sofi et al.²⁰⁹ was an update to the 2008 review conducted by the same author. This updated review investigated the association between adherence to the Mediterranean diet and a number of outcomes including mortality, Alzheimer's disease, mild cognitive impairment, coronary heart disease, cardiovascular disease, and gastric adenocarcinoma.²⁰⁹ The updated review identified one study²¹⁰ focused on the risk of AD. The study examined 1410 subjects, 66 of which developed AD over seven years of follow-up. Methods for categorizing exposure status were consistent with those used in the original review. The criteria used for the diagnosis of AD was not specified. A meta-analysis examining the effect of the Mediterranean diet on the incidence of neurological conditions (AD and Parkinson's disease) was conducted.²⁰⁹ Because the results of the meta-analysis were not specific to the outcome of AD, findings of the quantitative analysis will not be presented.

The reviewers converted results from included studies to reflect a two point increase in Mediterranean diet adherence score.²⁰⁹ The prospective cohort study²¹⁰ failed to detect an association between a two-point increase in Mediterranean diet adherence score and risk of developing AD (RR: 1.00; CI 0.71, 1.40). Finally, there was no evidence of publication bias.²⁰⁹ As in the earlier review²⁰⁸, conclusions were drawn for the effect of Mediterranean diet adherence on the incidence of Parkinson's disease and AD combined. However, conclusions were not drawn for AD considered separately.

d) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Technology Assessment prepared by the Duke Evidence-based Practice Center reviewed the association between the Mediterranean diet and risk of AD.²⁰ The reviewers identified four publications^{207,210,211,212}, thereof which examined the same cohort^{207,211,212}. The three studies

reporting on the same cohort of subjects examined 1875 to 2258 subjects and 107 to 282 incident cases of AD were observed during periods of follow-up ranging from four to 5.4 years. The remaining study examined 1410 subjects, 66 of which developed AD over 7 years of follow-up. Studies adhered to the NINCDS-ADRDA or DSM diagnostic criteria for AD ascertainment.²⁰ Adherence to the Mediterranean diet was ascertained according to food frequency questionnaires.²⁰ Exposure status was then categorized according to a scoring system with higher combined scores indicating higher adherence.²⁰

The cohort study by Scarmeas et al.²⁰⁷ reported that the highest tertile of adherence was associated with a 40% reduced risk of AD (HR: 0.60; 95% CI: 0.42, 0.87). Each point increase in adherence score was significantly associated with AD risk (HR: 0.91; 95% CI: 0.83, 0.98). In a more recent publication by the same author using the same cohort, high adherence was associated with a statistically significant reduced risk of AD (HR: 0.60; 95% CI: 0.42, 0.87).²¹¹ The combined effect of high adherence to the Mediterranean diet and high physical activity yielded similar findings (HR: 0.65; 95% CI: 0.44, 0.96).²¹¹ Using the same cohort, Scarmeas et al.²¹² also examined the effect of the Mediterranean diet on risk of progression from MCI to AD. Compared to low adherence, both moderate (HR: 0.55; 95% CI: 0.34, 0.90) and high (HR: 0.52; 95% CI: 0.30, 0.91) adherence to the Mediterranean diet was associated with a statistically significant reduced risk of conversion from MCI to AD. The cohort study by Feart et al.²¹⁰ reported that moderate and high adherence to the Mediterranean diet were not associated with AD (*Moderate* - HR: 0.99; 95% CI: 0.51, 1.94. *High* - HR: 0.86; 95% CI: 0.39, 1.88).²⁰

Overall, three publications^{207,211,212} reporting on the same cohort detected a reduced risk of AD associated with adherence to the Mediterranean diet.²⁰ One study²¹⁰, reporting on a different cohort, reported no association. The reviewers concluded that while there was some evidence of an association, further research is required.²⁰

Discussion

Four systematic reviews reporting on the effect of the Mediterranean diet were identified. There was some primary study overlap across the four reviews. Each review captured one of the four publications included in the referent review²⁰. In total, four publications^{207,210,211,212} examining two unique cohorts were identified across the reviews. While there was some evidence that greater adherence to the Mediterranean diet was associated with a reduced risk of AD²⁰, these findings were

limited by a number of factors including the very few available primary studies and issues pertaining to the ascertainment of the exposure.^{20,208} Adherence to the Mediterranean diet was consistently ascertained according to self-reported responses across the included studies.²⁰ Self-reported dietary intake is often affected by perceptions of health which may lead to exposure measurement error.⁹² More specifically, studies have found that unhealthy foods are often underreported while consumption of healthy foods are overreported.⁹² Moreover, research suggests that use of food frequency questionnaires may also give rise to exposure measurement error as this tool is likely to underestimate the true association between the exposure and the outcome.¹⁵⁷ Finally, using a scoring system to measure adherence and subsequently categorize subjects by exposure status is “limited by subjectivity” which may contribute to exposure measurement error.²⁰⁸ The limited number of available studies precludes a conclusive statement regarding the association between the Mediterranean dietary pattern and risk of AD.

Table 14 – Mediterranean diet and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies^a	Results	Conclusion
Weih et al. ⁶² (2007)	Amstar Score: 6 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD.	January 1966 to June 2006	1. Medline 2. Embase 3. Cochrane Database 4. Current Contents	1	1 of 4	The only identified study detected a reduced risk of AD associated with the highest tertile of adherence to the Mediterranean diet (HR: 0.60; 95% CI: 0.40, 0.90)	Reviewers concluded that there was “good evidence...that Mediterranean diet...might be protective”. ⁶²
Sofi et al. ²⁰⁸ (2008)	Amstar score: 6 Publication Bias Assessed: Yes	To investigate the association between adherence to a Mediterranean diet and mortality, Alzheimer's disease, cancer, and Parkinson's disease.	All years from inception of the databases up to 30 June 2008	1. PubMed 2. Embase 3. Web of Science 4. Cochrane Central Register of Controlled Trials	1	1 of 4	The only identified study detected a protective effect associated with a two-point increase in Mediterranean diet adherence score (RR 0.83; CI 0.70, 0.98)	No conclusions were drawn by authors for AD

Sofi et al. ²⁰⁹ (2010)	Amstar score: 9 Publication Bias Assessed: Yes	To investigate the association between adherence to a Mediterranean diet and health outcomes such as mortality, Alzheimer's disease, cancer, cardiovascular disease, coronary heart disease, and Mild cognitive impairment.	All years from inception of the databases up to June 2010	1. Medline 2. Embase 3. Web of Science 4. Cochrane Library 5. clinicaltrials.org 6. GoogleScholar	1	1 of 4	The only identified study failed to detect an association between a two-point increase in Mediterranean diet score and risk of AD (RR: 1.00; 95% CI: 0.71, 1.40).	No conclusions were drawn by authors for AD
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of Mediterranean diet	To examine the effect of several factors on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	4	Referent	Three of the four identified cohort studies detected a reduced risk of AD associated with adherence to the Mediterranean diet	Some evidence of an association between Mediterranean diet adherence and a reduced risk of AD.

^a "Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent". Item adopted from White et al.⁵¹

3.10 Fat intake/Saturated fatty acids

High consumption of saturated fats is a putative risk factor for the development of AD.²¹³ The detrimental effect of dietary saturated fats is linked to AD pathogenesis as it contributes to beta-amyloid plaque formation by way of elevated low-density lipoprotein and subsequent hypercholesterolemia.²¹³

Four moderate quality systematic reviews^{20,62,64,214} which examined the association between total fat, saturated fat, or transunsaturated fat intake and risk of AD were identified. Results of these reviews are qualitatively summarized.

a) Study: Weih et al.⁶²

Year: 2007

AMSTAR score: 6

Three cohort studies, reported in four publications^{146,148,215,216} identified in the systematic review by Weih et al.⁶² examined the association between fat intake and risk of AD. Excluding the earlier of two publications reporting on the same study¹⁴⁶, the remaining three observed an aggregate of 519 cases of AD (N = 7190) during periods of follow-up ranging from 3.9 to six years. Exposure status was ascertained according to semi-quantitative food frequency questionnaires.⁶² AD was consistently diagnosed according to the NINCDS-ADRDA criteria. A pooled analysis of the identified evidence was not conducted.

All three studies examining total fat intake and risk of AD reported no association (*Luchsinger et al.*²¹⁵ - RR: 1.40; 95% CI: 0.93, 2.13. *Engelhardt et al.*¹⁴⁸ - OR: 0.86; 95% CI: 0.73, 1.01. *Morris et al.*²¹⁶ - RR: 0.90; 95% CI: 0.40, 1.80). One²¹⁶ of two studies detected an increased risk of AD associated with high saturated fat intake (*Morris et al.*²¹⁶ - RR: 2.20; 95% CI: 1.10, 4.70. *Kalmijn et al.*¹⁴⁶ - OR: 1.90; 95% CI: 0.90, 4.00). The same study also reported an increased risk of AD associated with higher transunsaturated fat intake (*Morris et al.*²¹⁶ - RR: 2.40; 95% CI: 1.10, 5.30). Dietary cholesterol was not associated with risk of AD according to the only study²¹⁶ to report on the association (RR: 0.90; 95% CI: 0.40, 2.40). Despite the limited evidence, the reviewers concluded “that high...fat intake (total, saturated and transunsaturated fat) intake ...increases AD risk”.⁶²

b) Study: Crichton et al.²¹⁴

Year: 2010

AMSTAR score: 4

The systematic review by Crichton et al.²¹⁴ examined the association between fat intake from dairy products and risk of AD. The reviewers identified a single study²¹⁷ which focused on the risk of developing AD. The prospective cohort study examined 1449 subjects, 48 of which developed AD over 21 years of follow-up. The study examined the effect of fats obtained from dairy products, namely, “milk, sour milk, and spreads”.²¹⁴ Exposure status was ascertained according to self-reported responses to a food frequency questionnaire.²¹⁴ Finally, AD was ascertained using the DSM-IV criteria. Results from the CAIDE²¹⁷ study suggested that fat intake from milk or sour milk was not associated with risk of AD (OR not reported in review). However, the second quartile of saturated fatty acids from spreads was associated with increased risk of AD (OR: 3.82; 95% CI: 1.48, 9.87).

c) Study: Lee et al.⁶⁴

Year: 2010

AMSTAR score: 4

The review by Lee et al. examined the association between a number of lifestyle-related risk factors and AD.⁶⁴ Two publications^{133,217}, reporting on the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) cohort, examined the association between saturated fatty acids obtained from spreads and risk of AD. The CAIDE cohort included 1449 subjects, 48 of which developed AD over 21 years of follow-up. The second quartile of saturated fatty acid intake from spreads was associated with an increased risk of AD according to one publication²¹⁷ (OR presented in section b). Also reporting on the CAIDE cohort, the second publication¹³³ reported that higher saturated fatty acid consumption from spreads was associated with an increased risk of AD among APOE e4 carriers (OR: 4.34; 95% CI: 1.28, 14.68). The reviewers concluded that there was “consistent evidence of a...negative effect for high saturated fat intake...”.⁶⁴

d) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Health Technology Assessment (HTA) prepared for the US Agency for Healthcare Research and Quality examined the effect of medical, social/behavioural, environmental, dietary, and pharmacological factors on the risk of AD.²⁰ Two identified cohort studies^{216,217} examined the association between dietary fats (saturated, monounsaturated, transunsaturated) and risk of AD. The studies observed an aggregate of 179 cases of AD (N = 2264) during periods of follow-up ranging from 3.9 to 21 years. Outcome ascertainment was achieved according to DSM and/or NINCDS-ADRDA criteria.²⁰ The exposure was ascertained according to self-reported data.²⁰

Both studies reported an increased risk of AD associated with high²¹⁶ or moderate²¹⁷ saturated fat intake (RR/ORs presented in sections a and b). The only study²¹⁶ to report on high transunsaturated fat consumption reported an increased risk of AD (RR presented in section a). Total and monounsaturated fats were unassociated with risk of AD according to both studies (*Total fat* – RR for one study²¹⁶ reported in section a. RR for second study²¹⁷ not reported in review. *Monounsaturated fatty acids* – RRs not reported in review for both studies). Based on this evidence, the reviewers concluded that while there was some evidence of an association between saturated and transunsaturated fat consumption with an increased risk of AD, the available evidence was insufficient to draw definitive conclusions.²⁰

Discussion

Considered cumulatively, there was limited evidence to suggest that dietary saturated and transunsaturated fats are associated with an increased risk of AD.²⁰ The small number of available primary studies and limitations within these studies precludes any definitive conclusions. An important limitation involves the “broad category” of saturated fats considered.²¹⁸ This category includes subgroups of fats which exert differential effects. For example, while some saturated fats (e.g. lauric, myristic, and palmitic) have shown to increase low density lipoprotein (LDL), others exert no effect on cholesterol levels (e.g. stearic acid).²¹⁸ However, limiting intake and measuring

consumption of detrimental saturated fatty acids alone is difficult.²¹⁸ This may explain the treatment of saturated fatty acids as a broad exposure category by the available primary studies. By examining the effect of all saturated fatty acids, the observed detrimental association reported by some studies is likely diluted by the inclusion of “neutral effect”²¹⁸ saturated fats. Similarly, the lack of association reported by all four primary studies reporting on total fat intake is possibly related to the broad category of fats considered. More specifically, total fat intake includes consumption of putative protective (e.g. polyunsaturated fatty acids) and detrimental (e.g. saturated fatty acids, transunsaturated fatty acids) fats.¹⁴⁸ It is also possible that fat intake is not associated with AD. Finally, potential for reverse causation and selection bias must also be considered.

Table 15 – Saturated, transunsaturated, and total dietary fat and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies ^a	Results	Conclusion
Weih et al. ⁶² (2007)	Amstar Score: 6 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD.	January 1966 to June 2006	1. Medline 2. Embase 3. Cochrane Database 4. Current Contents	3	1 of 2	All three studies reported risk estimates exceeding 1.00. Only one study detected a statistically significant increased risk of AD associated with high saturated and transunsaturated fat intake	Dietary fat (saturated, transunsaturated) appeared to increase risk of AD.
Crichton et al. ²¹⁴ (2010)	Amstar Score: 4 Publication Bias Assessed: No	To evaluate the association between dairy consumption and cognitive function, AD, and dementia.	All years from inception of databases to July 2009.	1. Medline 2. Embase 3. Cinahl 4. PsychInfo 5. Web of Science	1	1 of 2	1. Fat intake from milk products: The only identified study failed to detect an association between fat intake from milk products and risk of AD. 2. Saturated Fatty Acids from spreads: The only identified study detected an increased risk of AD associated with	Results from the only identified study suggested that saturated fats from spreads may increase risk of AD.

							moderate intake of saturated fatty acids from spreads (OR: 3.82; 95% CI: 1.48, 9.87).	
Lee et al. ⁶⁴ (2010)	Amstar Score: 4 Publication Bias Assessed: No	To examine the effect of several factors on the risk of developing AD and other cognitive outcomes.	All years up to August 2008	1. Pubmed 2. Embase 3. PsychInfo	2	1 of 2	Both studies detected an increased risk of AD associated with high saturated fat.	Higher saturated fatty acid consumption was associated with an increased risk of AD
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of dietary fats.	To examine the effect of several factors on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	2	Referent	Both studies detected an increased risk of AD associated with high saturated fat. One study reported an increased risk associated with high transunsaturated fat. Both studies failed to detect an association between total and monounsaturated fats.	Saturated and transunsaturated fats may increase risk of AD.

^a "Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent". Item adopted from *White et al.*⁵¹

3.11 Caloric Intake

Reduced caloric intake may decrease risk of AD by reducing oxidative stress.²¹⁵ Two^{20,62} moderate quality systematic reviews examined the association between caloric intake and risk of AD.

a) Study: Weih et al.⁶²

Year: 2007

AMSTAR score: 6

Weih et al.⁶² identified a single cohort study that examined the association between caloric intake and risk of AD. The study examined 980 subjects, 242 of which developed AD over four years of follow-up. Exposure status was ascertained using a semi quantitative food frequency questionnaire and AD was diagnosed according to DSM-IV and NINCDS-ADRDA criteria.⁶² The study²¹⁵ reported a marginally significant 50% increased risk of AD associated with the highest quartile of caloric intake (RR: 1.50; 95% CI: 1.00, 2.20).

b) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Health Technology Assessment (HTA) reported by Williams et al.²⁰ identified the same study²¹⁵ captured by Weih et al.⁶² Again, high total daily caloric intake was associated with an increased risk of AD (HR: 1.48; 95% CI: 1.00, 2.19).²⁰ The reviewers concluded that results from a single study suggest an increased risk of AD associated with high caloric intake. However, the available evidence was deemed insufficient.²⁰

Discussion

A single cohort study reported an association between high caloric intake and risk of AD. Although both reviews relied on the same primary study, the extracted risk estimates and 95% confidence intervals varied slightly. The primary study²¹⁵ reported both risk estimates. More specifically, the risk estimate extracted by Williams et al.²⁰ was recorded in the results table while the risk estimate extracted by Weih et al.⁶² was presented in the abstract and body of the publication. Overall, the available evidence regarding the association between caloric intake and AD is inadequate.

Table 16 – Caloric intake and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies ^a	Results	Conclusion
Weih et al. ⁶² (2007)	Amstar Score: 6 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD.	January 1966 to June 2006	1. Medline 2. Embase 3. Cochrane Database 4. Current Contents	1	1 of 1	A single study detected an increased risk of AD associated with the highest quartile of caloric intake (RR: 1.50; 95% CI: 1.00, 2.20)	No conclusions drawn by authors
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of caloric intake	To examine the effect of several factors on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	1	Referent	Results from the only identified study suggest an increased risk of AD associated with high total daily caloric intake (HR: 1.48; 95% CI: 1.00, 2.19)	Available evidence was inadequate

^a "Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent". Item adopted from White et al.⁵¹

3.12 Education

Multiple pathways have been proposed to explain the observed protective association between higher educational attainment in early life and development of AD or dementia in late-life. According to the model adapted by Sharp et al., educational attainment is dependent on several factors, primarily, brain development.²¹⁹ Brain development is influenced by genetics, health and nutrition, environmental factors, as well as “parental socioemotional influence”.²¹⁹ In addition to brain development, parental socioeconomic status and “parental socioemotional influence” may have a direct effect on educational attainment.²¹⁹ Educational attainment may subsequently dictate socioeconomic status, environment, and behaviours in adulthood.^{219,220} Early-life factors guiding educational achievement as well as consequences of educational attainment (e.g. occupation) have also been linked to the development of AD in later-life.^{219,220} This has contributed to the hypothesis that the association between education and AD may be attributed to or explained by occupation or other aspects of socioeconomic status.²²⁰

The concept of cognitive reserve has been proposed as a potential explanation for the association between higher educational attainment and a reduced risk of AD.^{220,221} The cognitive reserve theory postulates that high educational attainment attenuates the clinical signs of AD-related brain pathology by activating alternate neural pathways in the presence of brain pathology.^{220,221} Greater cognitive reserve is indicative of superior morphological characteristics, namely, more neurons and neural connections.^{220,222} Greater cognitive reserve is also characterized by superior brain functionality, in other words, “greater overall cognitive efficiency”.²²² Cognitive efficiency is afforded by a compensatory mechanism which can be summarized as the involvement of intact neurons when initial neuronal communication is hampered by brain pathology (i.e. damaged neurons).^{220,221,222,223} Briefly, those with AD-related pathology can cope with neuronal injury as “communication” is carried through alternate, unaffected neural pathways.²²³

Greater cognitive reserve is attributed to higher cognitive capacity which is influenced by better brain development, particularly with respect to brain volume “early in life”.^{220,224} Cognitive capacity is also the sum of brain development throughout life.²²⁵ As such, other factors including educational attainment, occupation, and social engagement are purported to impact cognitive capacity.^{220,225,226} The concept of neuroplasticity, defined as the occurrence of morphological and functional brain changes “in response to stimuli”, is central to improvements in cognitive capacity and increases in cognitive reserve through the lifespan.^{223,227} Higher education results in, or is at least

suggestive (i.e. proxy) of, greater “reserves” of cognitive capacity which is essential for mitigating the effect of AD-related pathological changes.^{220,228,229} Although subjects with high educational attainment can be afflicted with brain pathology indicative of AD, they may not exhibit the clinical characteristics of the disease.^{220,221} This is afforded by greater reserve which allows one to “function for longer in the presence of brain pathology than a person with lower reserve”.²²⁰

The cognitive reserve theory is supported by studies which have reported the absence of or at least “fewer symptoms” among highly educated subjects despite the presence of pathological injury.^{220,228}

The association between education and AD may also be explained by other factors. Lower education, for example, is associated with putative risk factors for AD such as higher blood pressure and poorer nutrition.²³⁰ It is also hypothesized that the association between education and AD may be explained by intelligence, occupation and other aspects of socioeconomic status (page 156).

Three moderate-quality systematic reviews^{20,63,231}, which examined the association between education and risk of AD, were identified. One review³⁶, which scored two points on the AMSTAR assessment tool, was excluded due to low methodological quality. A total of sixteen primary studies^{74,76,114,232,233,234,235,236,237,238,239,240,241,242,243,286} were included across the three moderate-quality systematic reviews. Findings from these reviews are summarized below.

a) Study: Caamano-Isorna et al.²³¹

Year: 2006

AMSTAR score: 5

The systematic review and meta-analysis by Caamano-Isorna et al. examined the association between educational attainment and risk of AD.²³¹ A total of 14 studies were eligible for inclusion. Of these 14 studies, nine were cohort studies while five employed a case-control or nested case-control design. The cohort studies observed an aggregate of 1026 cases of AD (N=22724) during periods of follow-up ranging from one to 17 years. The case-control and nested case-control studies included 804 cases and 4905 controls. All 14 studies provided risk estimates comparing low education to high education. However, eight studies^{76,114,232,233,236,237,238,241} categorized educational status into tertiles, namely, low, moderate, or high levels of education. Included studies were heterogeneous with respect to the thresholds used to define each level of education.²³¹ Methods of exposure ascertainment were not specified. AD was consistently diagnosed according to the DSM-

III, DSM-IV, or NINCDS/ADRDA in all but one²³⁹ study. Statistical heterogeneity across included studies was assessed according to the Ri and Q statistic.²³¹ In the absence of heterogeneity, a fixed effects model was used to meta-analyze the data. A random effects model was employed in the presence of statistical heterogeneity. Publication bias was assessed by visual inspection of funnel plots and through a series of sensitivity analyses.²³¹

The reviewers conducted a meta-analysis comparing the risk of AD associated with the lowest level of educational attainment compared to the highest level of educational attainment. The pooled analysis, combining results of 14 studies, suggested that the lowest level of educational attainment was associated with an increased risk of AD (RR: 1.80; 95% CI: 1.43, 2.27). However, there was evidence of heterogeneity across the included studies (Ri statistic: 0.61; Cochrane Q statistic p-value: <0.0001). To examine potential methodological sources of the observed statistical heterogeneity, the reviewers conducted a subgroup analysis stratified by study design.²³¹ The pooled analysis of cohort studies detected an increased risk of AD associated with the lowest level of education (RR: 1.59; 95% CI: 1.35, 1.86; Ri statistic: 0.33; Cochrane Q statistic p-value: 0.157). The pooled analysis restricted to case-control studies also yielded statistically significant findings. However, the derived risk estimate was greater in magnitude (RR: 2.40; 95% CI: 1.32, 4.38). Results of the pooled analysis of case-control studies is likely an overestimation of the association between low educational attainment and AD which can be attributed to methodological limitations and sources of bias inherent in the case-control study design.^{71,98} There was also evidence of heterogeneity across the included case-control studies (Ri statistic: 0.79; Cochrane Q statistic p-value: 0.002).

A total of eight studies provided risk estimates for moderate levels of educational attainment. According to the pooled analysis, the combined category of low and moderate levels of education was associated with a significant increased risk of AD compared to the highest level of education (RR: 1.44; 95% CI: 1.24, 1.67; Ri statistic: 0.47; Cochrane Q statistic p-value: 0.073). The pooled risk estimate remained statistically significant when stratified by study design (*Cohort studies* - RR: 1.32; 95% CI: 1.09, 1.59; Ri statistic: 0.61; Cochrane Q statistic p-value: 0.0550; *Case-control studies* - RR: 1.66; 95% CI: 1.30, 2.10; Ri statistic: 0.00; Cochrane Q statistic p-value: 0.515). Finally, visual inspection of funnel plots and sensitivity analyses showed no signs of publication bias.²³¹

Based on the available evidence, the reviewers concluded that low educational attainment was associated with an increased risk of AD.²³¹ The analysis which combined the categories of low

and moderate levels of education yielded consistent findings suggesting an increased risk of AD attributed to low and moderate levels of education when compared to high educational attainment.²³¹

b) Study: Patterson et al.⁶³

Year: 2007

AMSTAR score: 4

The systematic review reported by Patterson et al. identified a single cohort study²³⁶ which was also included in the review reported by Caamano-Isorna²³¹. The study included 2356 subjects, 151 of which developed AD. The study reported a decreased risk of AD associated with lower educational attainment (<12 years versus. >15 years - RR: 0.48; 95% CI: 0.27 to 0.84). No conclusions regarding the effect of education on risk of AD were drawn by the reviewers.

c) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Health Technology Assessment (HTA), prepared for the US Agency for Healthcare Research and Quality, identified one systematic review²³¹ and two^{242,243} cohort studies which examined the association between educational attainment and risk of AD. The cohort studies included in the systematic review reported by Caamano-Isorna et al.²³¹ observed an aggregate of 1026 cases of AD (N=22724) during periods of follow-up ranging from one to 17 years. The two additional cohort studies identified by Williams et al.²⁰ examined an aggregate of 2470 subjects over periods of follow-up ranging from one to 21 years. One study²⁴² reported 48 incident cases of AD. The number of incident cases observed was not reported in the second study.

According to the findings of the identified systematic review by Caamano-Isorna et al.²³¹, low levels of education were associated with an increased risk of AD.²⁰ Findings from two cohort studies, published after the review by Caamano-Isorna et al.²³¹, reported consistent findings (≥ 9 years versus ≤ 5 years²⁴² - OR: 0.15; 95% CI: 0.05, 0.40. $\leq$ High school versus graduate school²⁴³ -

OR: 41.48; 95% CI: 4.00, 42.40). Based on the evidence provided by the included systematic review and cohort studies, the reviewers concluded that higher educational attainment was associated with a reduced risk of AD.²⁰ However, the reviewers acknowledged that the strength of evidence was low.

Discussion

Findings from three moderate-quality systematic reviews, collating evidence from 16 observational studies, suggested that lower levels of education, indicated by fewer years of education, was associated with an increased risk of AD. Findings of the identified reviews were limited by heterogeneity across included studies with respect to the thresholds used to categorize levels of education.²³¹

As previously described, the association between education and AD may be attributed to or explained by occupation or other aspects of socioeconomic status.²²⁰ However, evidence suggests that these factors do not entirely contribute to the observed association.²²⁰ Using data from the Canadian Study of Health and Aging, McDowell et al. reported that education remained associated with AD even after adjusting for socioeconomic status and occupation.²²⁰ Education is also linked to other components of cognitive reserve, namely innate and acquired intelligence.²²⁰ More specifically, those with higher innate intelligence are more likely to “obtain more education, which in turn increases [intelligence]”.²⁴⁴ As such, the association between education and AD may be explained by intelligence.²²⁰ Results from the Canadian Study of Health and Aging suggested that while intelligence accounted for some of the association, education remained associated with AD independent of intelligence.²²⁰

Issues relating to ascertainment error and other potential sources of bias must also be considered. Although self-reported data may give rise to measurement error, ascertainment of educational background according to self-report is consistent with conventional research practice.²⁰ A potential explanation for the association posits that tools for outcome ascertainment may be inadequate (i.e. “insensitive”) for “[identifying] impairment among those with high education”.²⁰ Results of the Canadian Study of Health and Aging did lend evidence to suggest that higher educated subjects tended to perform better on neuropsychological tests irrespective of cognitive status.²²⁰ However, this did not entirely explain the increased risk of AD associated with lower educational attainment.²²⁰

Other explanations for the observed association, such as the potential for selection bias, must be considered.²²⁰ In cohort studies, selection bias occurs when refusal to participate or losses to follow-up are associated with both the exposure and outcome of interest.²⁴⁵ If loss to follow-up is associated with low education, as research suggests, and low education is associated with a higher risk of AD, differential loss to follow-up would likely bias the association between low education and risk of AD towards the null.²²⁰ According to the Canadian Study of Health and Aging, however, losses to follow-up did not explain the association.²²⁰

Because the HTA relied on the earlier review by Caamano-Isorna et al.²³¹, there is significant overlap across the two reviews. Of particular interest is that the review by Patterson et al.⁶³ failed to include all nine cohort studies captured by Caamano-Isorna et al.²³¹, despite the similar range of years searched. As described in several sections of the present report, low primary study overlap may be attributed to the search strategy (e.g. generic versus specific exposure search terms) as well as differences in the eligibility criteria across reviews.

Overall, the available evidence is suggestive of a reduced risk of AD associated with higher educational attainment. According to the cognitive reserve hypothesis, greater cognitive reserve attributed to or measured by higher education may postpone the onset of clinically detectable AD.^{220,223} Worse brain damage upon diagnosis and faster cognitive decline observed among those with higher education serve as evidential support for the cognitive reserve hypothesis.^{220,246} Whether educational attainment is a true risk factor for AD or a factor involved in the postponement of clinical symptoms is of continued debate.^{221,231}

Table 17 – Educational attainment and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies^a	Results	Conclusion
Caamano-Isorna et al. ²³¹ (2006)	Amstar score: 5 Publication Bias Assessed, Test for Publication Bias, Result of test: (a) Publication Bias Assessed, Funnel Plot, No evidence of publication bias	To investigate the association between education and Alzheimer's disease, non-Alzheimer's dementia, and all dementias.	All years up to October 2005	1. Medline 2. Embase 3. PsychInfo 4. Scopus	14	0 of 2	1. Low vs. High: (RR: 1.80; 95% CI: 1.43, 2.27; Ri statistic: 0.61; Cochrane Q p-value: <0.0001). 2. Low vs. High – Cohort studies: (RR: 1.59; 95% CI: 1.35, 1.86; Ri statistic: 0.33; Cochrane Q statistic p-value: 0.157) 3. Low vs. High – Case-control studies: (RR: 2.40; 95% CI: 1.32, 4.38; Ri statistic: 0.79; Cochrane Q statistic p-value: 0.002). 4. Low and Moderate vs. High: (RR: 1.44;	Low educational attainment appears to increase risk of AD.

							95% CI: 1.24, 1.67; Ri statistic: 0.47; Cochrane Q statistic p-value: 0.0730) 5. Low and Moderate vs. High – Cohort studies: (RR: 1.32; 95% CI: 1.09, 1.59; Ri statistic: 0.61; Cochrane Q statistic p-value: 0.055). 6. Low and Moderate vs. High – Case-control studies: (RR: 1.66; 95% CI: 1.30, 2.10; Ri statistic: 0.00; Cochrane Q p-value: 0.515).	
Patterson et al. ⁶³ (2007)	Amstar Score: 4 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD and other cognitive outcomes.	1966 to December 2005	1. Medline 2. Embase	1	0 of 2	The only identified study reported a reduced risk of AD associated with more years of education (RR: 0.48; 95% CI: 0.27 to 0.84).	No conclusions drawn by author.
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of educational attainment	To examine the effect of several factors on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	2 (+relied on review by Caamano-Isorna)	Referent	Report identified one systematic review by Caamano-Isorna et al. and two cohort studies. The identified systematic review detected an increased risk of AD associated with low educational attainment	High educational attainment appears to reduce risk of AD.

							(see Caamano-Isorna et al. results summarized above for details). Both identified cohort studies detected an increased risk of AD associated with low levels of education.	

^a“Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent”. Item adopted from *White et al.*⁵¹

3.13 Cognitive Leisure Activities

The cognitive reserve hypothesis (see section 3.12) has also been suggested as a plausible mechanism to explain the putative beneficial effect of cognitively stimulating activities.^{42,62} Regular engagement in cognitively stimulating activities, as well as regular physical activity and social contact, constitute an “enriched environment” which is believed to enhance cognitive capacity and increase cognitive reserve.^{247,248} As previously described, the cognitive reserve hypothesis postulates that improvements in cognitive reserve allow for the postponement of AD-related symptomology irrespective of the degree of brain pathology.^{220,228} Engagement in cognitive activities facilitates neuroplasticity (i.e. “neurogenesis and synaptogenesis”) and increases cognitive reserve.^{228,249} Aside from delaying symptom onset, research also indicates that social engagement and participation in cognitive and physical activities can impact the etiological process by “[preventing or slowing] the accumulation of AD pathology”.²⁵⁰ Mitigation of stress afforded by such activities is a potential pathway by which AD is prevented.^{62,251}

A systematic search of the literature identified three moderate-^{20,42,62} and two low-^{36,251} quality systematic reviews which examined the association between cognitively stimulating leisure activities and subsequent risk of AD.

a) Study: Weih et al.⁶²

Year: 2007

AMSTAR score: 6

The systematic review by Weih et al. examined the effect of cognitive leisure activities on the risk of developing AD.⁶² In the event that a systematic review was identified, reviewers indicated that “further literature search was stopped”. The reviewers identified one²⁵¹ systematic review. As such, it appears that Weih et al. relied on five primary studies^{252,253,254,255,256} captured in the identified review. One²⁵² of the studies solely reported on all-cause dementia. The remaining four studies observed an aggregate of 464 cases of AD (N=3877) over a follow-up period ranging from 2.9 to five years. The exposures under examination in each of the included primary studies were not adequately described by Weih et al. All four primary studies reporting on risk of AD associated with cognitive leisure activities detected a statistically significant association (*Scarmeas et*

*al.*²⁵³ – RR: 0.62; 95% CI: 0.46, 0.83. *Wilson et al.*²⁵⁴ – OR: 0.36; 95% CI: 0.20, 0.65. *Wilson et al.*²⁵⁵ – HR: 0.67; 95%CI: 0.49, 0.92. *Verghese et al.*²⁵⁶ - HR: 0.93; 95% CI: 0.90, 0.97). The reviewers concluded that an “active, mentally challenging, and social lifestyle might protect against cognitive decline and possibly also AD”.⁶²

b) Study: Stern et al.⁴²

Year: 2010

AMSTAR score: 5

The systematic review by Stern et al. examined the effect of early-, middle-, and late-life participation in cognitive leisure activities on the risk of AD.⁴² For the purpose of the review, cognitive leisure activities were defined as those “[requiring] a mental response from the person taking part in the activity”.⁴² Relevant activities included “reading, watching movies, playing board games, playing musical instruments”.⁴² Among the included studies, exposure status was ascertained according to self-reported responses. AD was diagnosed according to the NINCDS-ADRDA or DSM criteria. Identified studies were quality assessed according to the Joanna Briggs Institute (JBI) checklist for cohort/case-control designs.⁴² Methodological heterogeneity across the included studies precluded a meta-analysis.⁴² Five case-control studies, which included an aggregate of 759 cases and 1461 controls, were included. One cohort study²⁶² reported both a five-year and 10-year follow-up in which 92 (N=3024) and 81 (N=1203) new cases of AD were identified, respectively. The remaining five cohort studies observed an aggregate of 554 cases of AD (N = 4652) over a period of follow-up ranging from 2.9 to five years. Four of the studies^{253,254,255,256} included in the review were also captured in the earlier review reported by Weih et al.⁶²

Five case-control studies^{257,258,259,260,261} and one cohort study²⁶² examined the association between early and midlife (20 to 60 years of age) participation in cognitive leisure activities and risk of AD. All six studies found a statistically significant or marginally significant association between AD and at least one domain of cognitive leisure activity or with cognitive leisure activities considered as an all-encompassing category.⁴² Frequent engagement in cognitive leisure activities was associated with an increased risk of AD according to three studies (*Non-occupational activities*²⁵⁷ - OR: 3.85; 95% CI: 2.65, 5.58. *Reading*²⁶¹ - OR: 9.60; 95% CI: 4.20, 21.90. *Reading*

and writing²⁶² - RR: 4.18; 95% CI: 2.44, 7.15). Regular engagement in mentally stimulating activities during midlife was associated with a reduced risk in three studies (*Novelty seeking activities*²⁵⁸ - OR: 0.25; 97.5% CI: 0.14, 0.44. *Activities involving discussion of ideas*²⁵⁸ - OR: 0.70; 97.5% CI: 0.47, 1.03. *Intellectually stimulating activities*²⁶⁰ - OR: 0.84; 95% CI: 0.72, 0.98. *Leisure activities*²⁵⁹ - OR: 0.54; 95% CI: 0.29, 1.00). One of two studies reported an association between television watching and AD (*Per hour increase*²⁶⁰ - OR: 1.32; 95% CI: 1.08, 1.62. *Not watching television*²⁶² - RR: 1.53; 95% CI: 0.82, 2.85).

A total of five^{253,254,255,256,263} cohort studies, which examined the association between late-life participation (≥ 65 years of age) in cognitive leisure activities and risk of AD, were eligible for inclusion in the systematic review. All five studies reported a reduced risk of AD associated with frequent engagement in cognitive leisure activities in late-life (*One-point increase in cognitive activity score*²⁵⁵ - HR: 0.67; 95% CI: 0.49, 0.92. *One-point increase in cognitive activity score*²⁵⁴ - OR: 0.36; 95% CI: 0.20, 0.65. *One-point increase in cognitive activity score*²⁵⁶ - HR: 0.93; 95% CI: 0.90, 0.97. *Frequent participation in cognitive activities*²⁶³ - HR: 0.58; 95% CI: 0.44, 0.77. *Frequent participation in cognitive activities*²⁵³ - RR: 0.62; 95% CI: 0.46, 0.83).

Based on the available evidence, the reviewers concluded that mid- and late-life participation in cognitive leisure activities was associated with a reduced risk of AD.⁴²

c) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Health Technology Assessment (HTA) reported by Wilson et al. examined the association between participation in cognitive leisure activities and risk of AD.²⁰ Four^{255,256,263,264} cohort studies were identified and included in the review. These studies observed an aggregate of 367 cases of AD (N = 7723) over a duration of three to five years. Cognitive leisure activities included, but were not limited to, reading, watching television, playing a musical instrument, and playing games (e.g. chess, checkers, puzzles, board games, cards).²⁰ Exposure status was ascertained according to self-report.²⁰ AD was consistently diagnosed according to NINCDS-ADRDA and DSM criteria.²⁰ All studies reported a statistically significant reduced risk of AD associated with regular

engagement in cognitively stimulating activities (RRs for three studies^{255,256,263} presented in sections a and/or b. *Highest tertile of activity*²⁶⁴ – HR: 0.39; 95% CI: 0.21 to 0.71). Based on the available evidence, the reviewers concluded that the evidence was suggestive of a reduced risk of AD associated with frequent participation.²⁰

Discussion

According to evidence summarized in three moderate-quality systematic reviews, increased participation in cognitive leisure activities appears to be associated with a reduced risk of AD. Due to primary study overlap, results of the systematic reviews are non-independent. The extent of primary study overlap is summarized in Table 18. The most recent review with the highest number of included studies served as the referent⁴². The referent review⁴² included the greatest number of studies as both cohort and case-control studies were eligible for inclusion. The remaining reviews restricted inclusion to cohort studies. The referent review captured all four studies included by Weih et al.⁶² and three of four studies included by Williams et al.²⁰

Results of these reviews are limited by potential sources of bias in the primary studies. Although the use of proxy informants is often a necessity in AD research, data collected by proxy informants may contribute to recall error.^{42,72} Secondly, the reviews are limited by heterogeneity across the included studies with respect to the definition of the exposure and the types of cognitive activities analyzed.^{20,42} Thirdly, variability in the degree of confounding adjustment across the included studies may have given rise to methodological heterogeneity.⁴² More specifically, there was heterogeneity across included observational studies with respect to the controlled covariates and the rigor of confounding adjustment.⁴² Results of the reviews may also be limited by the potential for reverse causation.⁴² Rather than causing AD, infrequent participation in cognitive activities may be a result of cognitive impairment due to “preclinical dementia”.⁴² That is, presence of preclinical dementia may alter exposure status. Those with preclinical AD or dementia may reduce the frequency at which they participate in cognitive leisure activities due to the onset of memory and cognitive deficits.⁴² Consequently, studies which fail to adequately exclude participants with preclinical dementia are susceptible to bias due to reverse causation.⁴² A number of studies accounted for this bias thereby minimizing the potential for reverse causation.⁴²

The association between cognitive activity and risk of AD may also be explained by higher educational attainment or intelligence.²⁶⁵ However, research suggests that “higher educational and occupational attainment and leisure activities” are independently associated with cognitive reserve and AD.^{220,250} For example, in the Canadian Study of Health and Aging, never working was associated with an increased risk of AD as compared to employment in cognitively stimulating occupations (i.e. “managerial or professional positions”) among highly educated subjects.²²⁰ Other studies have also suggested that educational attainment does not entirely explain the association between cognitive activities and AD.²⁶⁵

Overall, the available evidence suggests that frequent participation in cognitive leisure activities may be associated with a reduced risk of AD. However, these findings are derived from observational studies which are susceptible to several sources of bias.⁴² Large scale randomized controlled trials are warranted to validate these findings.⁴² Finally, while the evidence shows an association, participation in leisure activities may delay the onset or “expression” of clinical symptoms rather than prevent the etiological process.^{220,228,249}

Table 18 – Cognitive leisure activities and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies ^a	Results	Conclusion
Weih et al. ⁶² (2007)	Amstar Score: 6 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD.	January 1966 to June 2006	1. Medline 2. Embase 3. Cochrane Database 4. Current Contents	4	4 of 11	Identified one systematic review. Relied on five cohort studies (four reporting on AD) which were reported in the identified review. All four studies reported a statistically significant association.	An “active, mentally challenging, and social lifestyle might protect against cognitive decline and possibly also AD”. ⁶²
Stern et al. ⁴² (2010)	Amstar score: 5 Publication Bias Assessed: No	To investigate the association between participation in cognitive leisure activities and AD risk.	All years from inception of databases to September 2008	1. Medline 2. PubMed 3. Embase 4. Cinahl 5. PsychInfo 6. Cochrane Central Register of Controlled Trials (CENTRAL) 7. EBM Reviews 8. Current Contents 9. Education Resources	11	Referent	1. Midlife participation: All six studies found a statistically significant or marginally significant association between cognitive leisure activities and risk of AD. 2. Participation in late-life: All three studies	Middle and late-life participation in cognitive leisure activities “may be beneficial in preventing the risk of Alzheimer’s disease..”

				Information Center (ERIC) 10. Austhealth, Health Source: Nursing/Academic Edition 11. Scopus 12. Ageline 13. Scirus 14. Proquest Dissertations and Theses 15. Index to Theses 16. The Networked Digital Library of Theses and Dissertations (NDLTD) 17. Theses Canada			(reporting on AD) consistently reported that frequent engagement in cognitive leisure activities in late-life was protective against the development of AD.	
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of cognitive activities	To examine the effect of several factors on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	4	3 of 11	All four studies consistently detected a statistically significant reduced risk of AD associated with frequent participation in cognitive leisure activities	Increased participation in cognitive leisure activities was associated with a reduced risk of AD.

^a“Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent”. Item adopted from White et al.⁵¹

3.14 Physical Activity

Several biological mechanisms have been hypothesized to explain the putative protective effect of physical activity against the development of AD.²⁶⁶ Firstly, physical activity mitigates the neurodegenerative effect of vascular risk factors for AD, namely, hypertension and obesity.^{266,267} There is also evidence to suggest that engagement in physical activity exerts anti-inflammatory benefits and may reduce beta-amyloid plaque formation, both pathological attributes of AD.^{266,267} Finally, as a component of an “enriched environment”, physical activity is believed to produce neuroplastic alterations in the brain.^{247,248} There is evidence to suggest that physical activity promotes increases in brain volume, particularly in regions associated with AD (i.e. prefrontal and hippocampal areas).²⁶⁸ Increases in capillary volume have also been noted in animal models.²⁶⁹ Activity induced neuroplastic changes are linked with increases in cognitive reserve which results in the delayed onset of AD-related symptomology.^{228,249}

A review of the literature identified fifteen eligible systematic reviews^{20,36,59,60,62,63,64,251,266,267,270,271,272,273,274}. Six reviews^{36,59,60,251,271,274}, one³⁶ of which was an overview of reviews, were deemed to be of low methodological quality according to the AMSTAR criteria. Data was abstracted from nine moderate quality systematic reviews and results were qualitatively synthesized.

a) Study: Podewils²⁷⁰

Year: 2003

AMSTAR score: 7

The effect of physical activity on risk of all-cause dementia, AD, and vascular dementia was examined in the systematic review and meta-analysis by Podewils.²⁷⁰ Studies were identified through a database search of Medline, Cinahl, and PsycINFO. The search was supplemented with handsearching of journals and reference lists of pertinent studies.²⁷⁰ Duplicate, independent study screening and data extraction was conducted to minimize the potential for bias and transcription error. The methodological quality of included studies was examined according to a number of criteria, namely: sampling strategy, methods for exposure/outcome assessment, adequacy of confounding adjustment, and appropriateness of the statistical analyses.²⁷⁰ Statistical heterogeneity

was examined and studies were pooled according to the random effects model in the presence of significant heterogeneity.²⁷⁰ Otherwise, a fixed effects model was employed. If studies reported on the risk of all-cause dementia, the reviewers used this data in the analysis of AD. Pooled risk estimates were stratified by methodological design. Publication bias was assessed according to visual inspection of funnel plots.²⁷⁰

Five cohort^{74,275,276,277,278}, two nested case-control^{279,280}, and four case-control studies^{101,257,261,281} were eligible for inclusion. The cohort studies observed an aggregate of 734 cases of dementia/AD (N=7056) over a period of follow-up ranging from 2.9 to seven years. The two nested case-control studies included an aggregate of 313 cases and 3930 controls. The four case-control studies included a total of 502 cases of dementia/AD and 1006 controls. Studies were heterogeneous with respect to the definition (i.e. type, frequency, intensity) and categorization of the exposure under study.²⁷⁰ Dementia and AD were consistently diagnosed according to the DSM and NINCDS-ADRDA criteria. To improve appropriateness for pooling, the active versus inactive comparison was considered.²⁷⁰ According to the random effects meta-analysis, physical activity was protective for AD according to analyses restricted to cohort and case-control studies, respectively (*Cohort studies* - RR: 0.59; 95% CI: 0.42, 0.77; *Case-control studies* - OR: 0.24; 95% CI: 0.09, 0.60). Visual inspection of funnel plots indicated the presence of publication bias.²⁷⁰ Statistical methods to address the presence of bias were not employed.

Based on the available evidence, the reviewer concluded that engagement in physical activity protected against AD.²⁷⁰ The review was limited by sources of methodological heterogeneity across studies with respect to the type, frequency, duration, and categorization of physical activity.²⁷⁰ Secondly, the review was susceptible to publication bias. The combination of studies reporting on all-cause dementia with those specifically examining AD must also be considered.²⁷⁰ All-cause dementia is a broad category which can encompass cognitive impairments of various etiologies.²⁷⁰ Consequently, the derived pooled risk estimates were not specific to AD.²⁷⁰ Finally, as noted by the reviewers, a number of studies failed to consider the effect of APOE e4 status.²⁷⁰

b) Study: Weih et al.⁶²

Year: 2007

AMSTAR score: 6

The systematic review by Weih et al. involved a search of Medline, Embase, Current Contents, and the Cochrane database.⁶² The search was supplemented by a review of www.clinicaltrialresults.org and of reference lists of pertinent papers. The review was restricted to longitudinal studies of disease-free populations.⁶² The Oxford Centre for Evidence-based Medicine criteria, which evaluates the strength of evidence for a given risk factor based on the methodological design of available studies, was used.⁶² A pooled analysis was not attempted.

The effect of physical activity on AD risk was investigated in seven studies reported in eight publications^{74,76,278,280,282,283,284,285}. Six cohort studies observed 705 cases of AD (N=8053) over a follow-up period ranging from 4.1 to seven years. The remaining publications^{76,280} reported on a nested case-control study which included 194 cases and 3894 controls. Exposure status was consistently ascertained according to self-reported responses to an interview or questionnaire.⁶² Further detail pertaining to the specific definitions of physical activity employed in the primary studies was not reported in the review. The DSM (III-R/IV) and/or the NINCDS-ADRDA criteria were used for outcome ascertainment. Two studies, reported in three publications, reported a reduced risk of AD associated with physical activity (*Physical activity*⁷⁴ – RR: 0.20; 95% CI: 0.06, 0.68. *Physical activity*⁷⁶ – RR: 0.69; 95% CI: 0.50, 0.96. ≥ 3 times/week²⁸⁰ – RR: 0.50; 95% CI: 0.28, 0.90). Five of the remaining studies reported risk estimates below 1.00. However, results failed to reach statistical significance (*Highest quartile*²⁷⁸ – RR: 0.61; 95% CI: 0.35, 1.05. *Weekly hours of physical activity*²⁸⁴ – RR: 1.04; 95% CI: 0.0.98, 1.10. *>16 points versus <9 points on physical activity scale*²⁸⁵ – RR: 1.27; 95% CI: 0.78, 2.06. *>1657 kcal/week*²⁸² – RR: 0.70; 95% CI: 0.44, 1.13. ≥ 3 times/week²⁸³ – RR: 0.69; 95% CI: 0.45, 1.05). The reviewers concluded that “physical activity may reduce AD risk”.⁶²

c) Study: Patterson et al.⁶³

Year: 2007

AMSTAR score: 4

The systematic review conducted by Patterson et al. examined the effect of several putative risk factors on the development of AD and other cognitive outcomes including unspecified and vascular dementia.⁶³ Studies were located using a search of Medline, Embase, and by reviewing the reference list of pertinent studies. Studies excluded by the primary reviewer were verified by three

reviewers.⁶³ Duplicate, independent quality assessment and data extraction were carried out. Longitudinal studies deemed to be of “fair” or “good” quality were eligible for inclusion.⁶³ Methodological quality was ascertained according to several criteria pertaining to the sampling strategy, exclusion of prevalent cases at baseline, completeness of follow-up, methods for exposure/outcome ascertainment, degree of confounding adjustment, and adequacy of the statistical analysis.⁶³

Two studies reported in three publications^{76,280,282} examined the association between physical activity and risk of AD. Two publications reported on a nested case-control study which included 194 cases and 3894 controls. The remaining cohort study observed 245 cases of AD (N=3375) over a follow-up of 5.4 years. Both studies reported a reduced risk of AD associated with regular or high levels of physical activity (≥ 4 activities²⁸² – RR: 0.55; 95% CI: 0.34, 0.88. RRs for two publications^{76,280} presented in section b). The reviewers concluded that these results are suggestive of a reduced risk of dementia associated with physical activity.⁶³

d) Study: Rolland et al.²⁷²

Year: 2008

AMSTAR score: 4

The effect of physical activity on risk of AD and other cognitive outcomes was reviewed by Rolland et al.²⁷² Studies were identified through a search of PubMed, Medline and BIOSIS.²⁷² The search was also supplemented by handsearching the relevant literature.²⁷² Inclusion was limited to longitudinal studies written in English.²⁷² A pooled analysis was not attempted. The methodological quality of identified studies was not examined. The presence of publication bias was not assessed.

Ten studies reported in eleven publications^{74,76,125,276,280,283,285,286,287,288,289} reported on the effect of physical activity on the risk of developing AD, although risk estimates specific to AD were not specified for a majority of studies. Nine cohort studies observed an aggregate of 735 cases of AD (N=11207) over a period of follow-up ranging from 2.9 to 30 years. The remaining two publications^{76,280} reported on a nested case-control study which included 194 cases and 3894 controls. The reviewers also identified one study²⁸² which reported on AD although the reviewers solely presented data pertaining to dementia. Six studies^{74,76,125,283,287,289} reported on the effect of physical activity treated as a broad category and three studies^{276,285,288} reported on the effect of a

specific measure of physical activity, namely, walking and dancing. One study²⁸⁶ reported on the effect of occupational attainment. It is assumed that the reviewers used occupational attainment as an indicator of physical activity.

Seven of the ten studies reported a statistically significant association between physical activity, or at least one measure of activity, and risk of AD/dementia.²⁷² Of the seven studies, five reported a reduced risk of AD associated with regular engagement in physical activities (*Walking*²⁷⁶ - RR: 0.73; 95% CI: 0.55, 0.98. *Dancing*²⁸⁵ - HR: 0.24; 95% CI: 0.06, 0.99. *Physical activity*²⁸⁹ - OR: 0.38; 95% CI: 0.17, 0.85. RRs for two studies^{74,76} presented in section b). One study each reported an increased risk of dementia or AD associated with low occupational attainment²⁸⁶ (assumed to serve as an indicator of activity) or lower levels of walking²⁸⁸ (*Low occupational attainment*²⁸⁶ - RR: 2.25; 95% CI: 1.32, 3.84. *Walking <0.25 miles/day*²⁸⁸ - RH for dementia: 1.77; 95% CI: 1.04, 3.01). The remaining three studies failed to detect a statistically significant reduced risk of AD associated with physical activity (RR for two studies not reported in the review^{125,287}. RR for remaining study²⁸³ presented in section b). Based on the available evidence, the reviewers concluded that physical activity was associated with a protective association against the development of AD and dementia.²⁷²

e) Study: Hamer et al.²⁶⁶

Year: 2009

AMSTAR score: 6

The effect of physical activity on the development of AD, all-cause dementia, and Parkinson's disease was reviewed by Hamer et al.²⁶⁶ Studies were retrieved from a Medline, Cochrane Database of Systematic Reviews, and Web of Science database search. The search was also supplemented by handsearching relevant articles. The review was restricted to prospective cohort studies published between 1990 and 2007 that ascertained exposure status at baseline. Methodological quality was examined according to the appropriateness of the methods used for exposure ascertainment and the adequacy of confounding adjustment.²⁶⁶ Heterogeneity across studies was examined according to the Cochrane Q-test and results were pooled according to the random effects model. Publication bias was explored using funnel plots and Begg's asymmetry test.²⁶⁶

Six studies^{74,280,282,284,288,289} were eligible for inclusion in the pooled analysis for AD. One study²⁸⁰ employed a nested case-control design in which 194 cases and 3894 controls were included in the analysis. The remaining studies were cohort studies which observed an aggregate of 603 cases of AD (N=8749) during follow-up periods ranging from 4.1 to 21 years. Studies were heterogeneous with respect to the definition of the exposure variable. The exposure of interest was broadly defined in five studies while the remaining study²⁸⁸ specifically examined the effect of walking. Studies also varied with respect to the duration, frequency and/ or intensity of physical activity under study.²⁶⁶

Five of six studies reported risk estimates below 1.00 for the highest category of physical activity. The definition of high physical activity varied across studies. Across studies, high physical activity was defined as participation in activities two times per week, participation in vigorous activities three times per week, daily physical activity, walking greater than two miles per day, or five hours of activity per week.²⁶⁶ Results of the random effects meta-analysis suggest that the highest category of physical activity engagement was associated with a 45% reduced risk of AD (RR: 0.55; 95% CI: 0.36, 0.84). Studies were statistically heterogeneous (Test for heterogeneity: $\chi^2 = 29.12$, $p < 0.001$). Subgroup analysis revealed that the association was more pronounced in methodologically rigorous studies. However, risk estimates for the subgroup analysis were not reported for AD.²⁶⁶ Finally, there was no indication of publication bias ($p > 0.10$).²⁶⁶ Overall, the reviewers concluded that physical activity was associated with a reduced risk of AD.²⁶⁶

f) Study: Stern et al.²⁶⁷

Year: 2009

AMSTAR score: 6

The systematic review by Stern et al. examined the effect of physical leisure activities on the prevention of all-cause dementia and AD.²⁶⁷ Studies were identified through an extensive database search (n=12) including, but not limited to, Medline, Cinahl, Embase, and Cochrane CENTRAL.²⁶⁷ The search was supplemented by a grey literature search (e.g. theses and dissertations) and a handsearch of the citations list of pertinent articles. Randomized controlled trials and observational studies (case-control, cohort, and cross-sectional) reporting on the effect of physical activities in preventing cognitive outcomes among elderly subjects were eligible for inclusion.²⁶⁷ Methodological quality was assessed according to the Joanna Briggs Institute

instrument which considers population characteristics, completeness of follow-up, potential for bias, appropriateness of statistical techniques, and adequacy of confounding adjustment.²⁶⁷ Heterogeneity across studies precluded a pooled analysis and the presence of publication bias was not explored.²⁶⁷

Two case-control^{257,261}, one nested case-control study²⁸⁰, and 10 cohort studies^{262,276,278,282,283,284,285,288,289,290} reporting on the risk of AD were eligible for inclusion. The nested case-control study²⁸⁰ included 194 AD cases and 3894 controls. The case-control studies included an aggregate of 253 cases and 478 controls. One cohort study²⁶² reported both a five-year and 10-year follow-up in which 92 (N=3024) and 81 (N=1203) new cases of AD were identified, respectively. The remaining nine cohort studies observed an aggregate of 1190 cases of AD (N= 15839) over a period of follow-up ranging from 2.9 to 31 years.

Three studies^{280,289,290} examined the effect of physical activity as a broadly defined category. The remaining studies investigated the effect of a heterogeneous list of activities including, but not limited to, sports, gardening, walking, jogging, golfing, swimming, housework, and cycling.²⁶⁷ Eight studies^{280,278,282,283,284,285,289,290} reported on the frequency of participation and four^{257,280,282,289} considered the intensity of physical activity. Four studies^{257,261,289,290} reporting on the risk of AD examined the effect of activities engaged in during midlife. One study²⁵⁷ reported on the effect of participation in early adulthood. The remaining studies reported on late-life physical activities. All studies employed acceptable criteria for outcome ascertainment; however, the specific instrument used in each study was not specified in the review.²⁶⁷

The only study²⁵⁷ that reported on activities during early adulthood determined that cases were less likely to have engaged in a range of activities when compared to controls suggesting that “physical diversity” in early adulthood may reduce risk of AD (OR: 2.67; 95% CI: 1.85, 3.85).²⁶⁷ With respect to activities engaged in during midlife, three of the four studies reporting on the risk of AD detected a protective association (*Regular activity*²⁹⁰ - OR: 0.34; 95% CI: 0.16, 0.72. OR for one study²⁶¹ not reported in review. OR for one study²⁸⁹ presented in section d). Finally, one case-control study²⁵⁷ failed to detect an association between AD and participation in physical activities in midlife (OR not reported in review).

Six of the nine studies reporting on the risk of AD associated with late-life engagement in physical activities detected an association between the variables of interest (RRs for four studies^{280,276,282,285} reported in sections b and d). Of the six studies, two reported an increased risk of AD associated with low physical activity or a sedentary lifestyle (RR for one study²⁶² not reported in review. RH for one study²⁸⁸ reported in section d). For one study²⁸³, reviewers reported the risk

estimate corresponding to dementia but not AD. According to data presented in other reviews^{62,272}, results of the study²⁸³ were not suggestive of an association with AD. The remaining three studies^{278,283,284} failed to detect an association between late-life engagement in physical activity and risk of AD (RRs presented in section b).

Considered cumulatively, the reviewers concluded that the available evidence did not consistently support a reduced risk of AD and all-cause dementia associated with physical activity participation.²⁶⁷ When the analysis was restricted to studies reporting on risk of AD specifically, three of four and six of nine studies reporting on midlife and late-life physical activities, respectively, detected an association. Results of the review are limited by sources of bias inherent in observational studies as well as heterogeneous (i.e. type, frequency, intensity) and often broad definitions of physical leisure activities.²⁶⁷ A majority of studies controlled for the effect of potentially confounding variables, however, the degree or rigor of confounding adjustment varied across studies.²⁶⁷

g) Study: Lee et al.⁶⁴

Year: 2010

AMSTAR score: 4

Lee et al. systematically reviewed the literature for longitudinal, community-cohort studies which examined the risk of AD associated with physical activity among elderly subjects (≥ 65 years).⁶⁴ Inclusion was restricted to studies of high methodological quality, which was established according to an assessment of several criteria, namely, sampling strategy, methods for exposure/outcome ascertainment, degree of confounding adjustment, and completeness of follow-up.⁶⁴

Studies varied with respect to the definition (i.e. type, frequency, duration) and categorization of the exposure variable. Six publications^{133,282,283,288,291,292} reported on the association between physical activity and AD. Two publications reported on the Cardiovascular risk factors, Aging and Incidence of Dementia (CAIDE) study^{133,292} and two reported on the Honolulu-Asia Aging Study (HAAS)^{288,291}. The CAIDE study^{133,292} included 1449 subjects, 48 of which were diagnosed with AD over 21 years of follow-up. Studies reporting on the HAAS cohort^{288,291} reported

83 and 101 incident cases of AD (N = 2257 or 2263) over six years of follow-up. The remaining two studies^{282,283} examined 4994 subjects with an aggregate of 352 cases of AD identified over 5.4 to 6.2 years of follow-up.

Of the six included publications, four reported a statistically significant association. Two studies detected a reduced risk of AD associated with high levels of physical activity (RR for one study²⁸² presented in section d. RR for second study²⁹¹ not reported in review). Two studies reported a statistically significant increased risk of AD associated with sedentariness and low levels of walking, respectively (RR for one study¹³³ not reported in review. *Walking < 0.25 miles/day*²⁸⁸ – RH for AD: 2.21; 95% CI: 1.06, 4.57). Regular exercise (≥ 3 times/week)²⁸³ and occupational physical activity (“total daily commuting physical activity”)²⁹² were not related to AD according to the remaining studies (RR for one study²⁸³ presented in section b. RR for second study²⁹² not reported in review). Based on the identified evidence, the reviewers concluded that physical activity appeared to “confer some protection against cognitive decline and dementia”.⁶⁴

h) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

The Health Technology Assessment (HTA), prepared for the US Agency for Healthcare Research and Quality, reviewed the available literature to examine the association between physical activity and subsequent risk of AD.²⁰ Medline and the Cochrane Database of Systematic Reviews were searched to identify relevant systematic reviews.²⁰ Identification of a methodologically sound systematic review was supplemented by a search of the literature to identify primary studies published after the given review (up to October 2009).²⁰ The quality of systematic reviews was examined according to criteria pertaining to the search strategy, eligibility criteria, quality assessment, statistical analyses, and the rigor to minimize bias.²⁰ Primary studies were quality assessed according to criteria put forth by the Agency for Healthcare Research and Quality (AHRQ), which takes into account the sampling strategy, methods for exposure/outcome ascertainment, degree of confounding adjustment, suitability of the statistical analyses, and thoroughness of reporting.²⁰

No systematic reviews satisfied the eligibility criteria. Therefore, the reviewers relied solely on primary studies.²⁰ Twelve studies^{74,211,280,282,283,285,288,289,290,292,293,294} were identified. Two studies, which recruited subjects from the same cohort, reported 76 and 48 incident cases of AD (N= 1449) over 21 years of follow-up.^{289,292} One study²⁸⁰ employed a nested case-control design including 194 AD cases and 3894 controls. In the remaining nine cohort studies, an aggregate 1194 cases of AD (N = 20122) were observed during periods of follow-up ranging from 3.9 to 31 years. Three^{289,290,292} studies examined the effect of participation in physical activities during midlife while the remaining studies examined activities undertaken in late-life.²⁰ Studies were heterogeneous with respect to the type of physical activity under investigation. While some studies examined the effect of physical activity as a broadly defined category, others examined the effect of a heterogeneous list of activities including, but not limited to, gardening, walking, jogging, golfing, swimming, housework, and cycling.²⁰ A clinical diagnosis of AD was achieved according to the DSM and/or NINCDS-ADRDA criteria in all studies.

Nine studies^{74,211,282,283,285,288,289,293,294} were eligible for inclusion in a pooled analysis. Six of the nine studies included in the pooled analysis reported risk estimates below 1.00. The pooled analysis detected a reduced risk of AD associated with physical activity (HR: 0.72; 95% CI: 0.53, 0.98).²⁰ However, there was evidence of statistical heterogeneity across studies ($Q = 23.25$, $p = 0.003$, $I^2 = 66\%$). With respect to the remaining three studies that were excluded from the pooled analysis, all detected a reduced risk of AD associated with moderate and/or high levels of physical activity. Based on the available evidence, the reviewers concluded that the identified evidence was suggestive of a reduced risk of AD associated with engagement in physical activities. As stated by the reviewers, the evidence was most convincing for high levels of activity.²⁰

i) Study: Weih et al.²⁷³

Year: 2010

AMSTAR score: 5

The effect of physical activity on risk of developing AD was reviewed by Weih et al.²⁷³ Studies were retrieved through a search of Medline and via handsearching the bibliographies of pertinent literature. Inclusion was restricted to prospective cohort studies which provided sufficient detail pertaining to the methods employed for exposure and outcome ascertainment. Furthermore,

only studies reporting risk estimates comparing active vs. inactive or low vs. high activity levels were considered. Physical activity was consistently ascertained according to self-reported responses to a questionnaire. Further detail pertaining to the specific definition of physical activity employed in the primary studies was not provided in the review. Methods employed for outcome ascertainment were not specified. Methodological quality of included studies was not examined. Heterogeneity across studies was evaluated according to the chi-squared test and I^2 index.²⁷³ Results were pooled according to fixed and random effects models and the presence of publication bias was assessed according to visual inspection of funnel plots.²⁷³

Six studies^{76,211,282,288,289,294} satisfied the inclusion criteria. As reported by the reviewers, an aggregate of 271 cases (N = 10 380) as observed during periods of follow-up ranging from 3.9 to 21 years.²⁷³ Five of six studies reported a statistically significant reduced risk of AD associated with high physical activity when compared to no or low levels of activity. The remaining study reported a risk estimate below 1.00, although it failed to reach statistical significance. According to the random effects meta-analysis, compared to sedentariness or low physical activity, engagement in high physical activity was associated with a reduced risk of AD (RR: 0.59; 95% CI: 0.50, 0.69). There was no evidence of statistical heterogeneity across studies (Test for heterogeneity: $\chi^2 = 1.84$, df = 5, $p = 0.87$). Although publication bias was evaluated, results of the assessment were not reported. In light of the meta-analytic results, the reviewers concluded that physical activity was associated with a reduced risk of AD.²⁷³

Discussion

Although not unanimous, the available evidence collated in moderate quality systematic reviews is suggestive of a reduced risk of AD associated with higher levels of physical activity. Despite methodological heterogeneity across reviews with respect to the comprehensiveness of the search strategies, rigor to minimize the potential for bias (i.e. duplicate, independent screening and data abstraction), and rigidity of the eligibility criteria, eight of nine identified systematic reviews concluded that engagement in physical activities was associated with a reduced risk of AD. Furthermore, all but two^{267,270} of the reviews were restricted to longitudinal studies which further validates the observed association.

Important study- and review-level limitations warrant a cautious interpretation of the results. Firstly, when experimental studies are lacking, systematic reviews are limited by sources of bias inherent in observational studies.^{267,272} Studies that require subjects to recall past exposures, particularly those that employ proxy informants, are prone to recall bias.^{71,72,267} Longitudinal cohort studies that fail to exclude cognitively impaired subjects at study outset are susceptible to reverse causality as physical activity levels may alter as a result of cognitive impairment.^{93,267,272} As noted by a number of reviewers, a majority of the available studies relied on exposure status ascertained solely at baseline.^{272,273} Longitudinal studies, particularly those with longer durations that fail to re-assess physical activity levels at follow-up may not accurately ascertain exposure status as engagement in activities may fluctuate over the course of the study.^{272,273} Most, if not all, primary studies also relied on self-reported data which may be prone to error.^{272,295} Research suggests that self-reported physical activity differs from data obtained through objective measures.²⁹⁵ This finding lends evidence to suggest that objectively measured physical activity would likely improve the accuracy of the collected data.²⁹⁵ Physical activity is also associated with other life-style risk factors for AD which makes it difficult to parse out the effect of physical activity alone.²⁷³ Finally, as noted in one of the reviews, some primary studies failed to consider the effect of APOE e4 status.²⁷⁰ Research suggests that APOE e4 status may modify the effect of physical activity on the development of AD.²⁹⁶ While physical activity has been associated with a reduced risk of dementia, AD, and vascular dementia among APOE e4 non-carriers, no significant association was detected for carriers.²⁹⁶

The identified systematic reviews are also limited by methodological heterogeneity across included studies with respect to the definition and categorization of the exposure variable.^{20,267,270} While some studies examined physical activity as a broad category, others collected data pertaining to participation in particular activities (e.g. walking, swimming, dancing).^{20,267} Studies also varied with respect to the frequency, duration, and/or intensity of physical activity being considered (i.e. 5 hours/week, 2 times/week, rigorous activity for 20-30 min/day).^{267,272} Furthermore, studies varied with respect to the categorization of the exposure variable with some studies treating physical activity as a dichotomous variable (i.e. active vs. sedentary) and others dividing exposure into tertiles (i.e. light, moderate, heavy) and quartiles. There was also evidence of heterogeneity across studies choosing to treat the exposure variable similarly (e.g. dichotomous variable) as different cut-offs or thresholds of physical activity were employed. Although exposure status was consistently ascertained according to self-report, primary studies varied with respect to the specific questionnaire

used to gather pertinent data. Studies also varied with respect to the timing of exposure ascertainment with some studies assessing physical activity levels in midlife and others in late-life.^{20,267} These sources of heterogeneity may at least partially explain the statistical heterogeneity observed in the systematic reviews attempting to quantitatively synthesize the evidence.^{20,266} Despite the sources of methodological heterogeneity, all four reviews with a meta-analytic component adequately assessed the presence of statistical heterogeneity and appropriately pooled results according to the random effects model, which takes heterogeneity into account.⁹¹ However, failure to conduct robust subgroup analyses, likely due to insufficient data from primary studies, precludes a definitive statement with respect to the specific clinical and/or methodological sources of the observed statistical heterogeneity.

For the most part, the identified systematic reviews yielded consistent findings. This is attributed to the significant overlap in primary studies across systematic reviews. Using the most recent review with the highest primary study yield as the referent²⁰, the extent of overlap ranged from two to seven studies. Reviews reported by Podewils et al.²⁷⁰ and Patterson et al.⁶³ captured only two of the twelve studies included by the referent²⁰. The small degree of overlap between the referent²⁰ and the review reported by Podewils et al.²⁷⁰ was expected as ten^{211,282,283,285,288,289,290,292,293,294} of the primary studies included in the referent were published after the Podewils et al.²⁷⁰ review (i.e. 2003 or later) and were therefore unavailable for inclusion. Six^{74,280,282,285,288,289} studies included in the referent²⁰ were published before December 2005 and should have been identified by Patterson et al.⁶³ However, only two^{280,282} of the six studies were included. While both reviews restricted inclusion to longitudinal cohort studies, other differences in eligibility criteria may explain the low overlap. Firstly, Patterson et al.⁶³ restricted inclusion to studies examining populations “representative of Canadian demographics”. Three of the four studies that were not included by Patterson et al.⁶³ solely examined Japanese⁷⁴, Japanese-American²⁸⁸, and Finnish²⁸⁹ populations. As these populations may not be representative of Canadian demographics, this may explain the exclusion of these studies. Secondly, while the quality of primary studies was appraised in both reviews, Patterson et al.⁶³ restricted inclusion to fair or good quality studies while the referent employed a more inclusive approach. While these factors may potentially explain the low level of overlap between the referent review²⁰ and that reported by Patterson et al.⁶³, reasons for the minimal overlap can only be speculated as Patterson et al.⁶³ failed to provide a list of excluded studies with clearly defined reasons for exclusion. It is also possible that failure to include the four studies is due to non-identification rather than exclusion. That is, the search strategy employed by

Patterson et al.⁶³ may not have captured the four studies in question. The search strategy employed in the referent review²⁰ incorporated risk factor-specific terminology (i.e. “exercise, physical fitness, running, swimming, walking”²⁰). As Patterson et al.⁶³ sought all modifiable risk factors for dementia, the employed search strategy was not tailored to solely identify literature pertaining to physical activity. As such, the reviewers relied on generic exposure search terms (i.e. “risk factor”). It is therefore possible that failure to incorporate exposure-specific terminology may have resulted in the oversight of primary studies indexed according physical activity-related medical subject headings.

Of particular interest, when compared to the referent²⁰, the review²⁶⁷ with the greatest primary study overlap (n=7) yielded discordant conclusions. Nine of 13 studies identified in the review²⁶⁷ reported a statistically significant beneficial association between physical activity and risk of AD. However, the reviewers concluded that the “evidence was equivocal”.²⁶⁷ Other reviews, which captured less convincing evidence, concluded that physical activity was associated with a reduced risk of AD. For example, of the six studies identified by Weih et al.⁶², only two studies (reported in three publications) detected a statistically significant reduced risk of AD. Despite the scarce evidence, the reviewers concluded that “there is good evidence...that physical activity may reduce AD risk...”.⁶² This example suggests that discordant conclusions across reviews may arise as a result of discordant “interpretations and inferences made by the review authors”.⁹⁰ That is, some review authors may employ a more conservative approach for interpreting the identified evidence and deriving conclusions.

Despite reliance on the same primary studies, data extracted from overlapping studies may have differed across reviews. For example, the Conselice Study of Brain Aging (CSBA)²⁹⁴ was included in reviews reported by Williams et al.²⁰ and Weih et al.²⁷³. Several risk estimates were reported in the primary study pertaining to “participation in different physical activities”²⁹⁴. The pooled analysis reported by Williams et al.²⁰ relied on the risk estimate pertaining to highest level of walking (>417 Kcal/week – HR: 1.42; 95% CI: 0.68, 2.97). Rather than relying on a specific domain of physical activity (i.e. walking), Weih et al.²⁷³ relied on data pertaining to total physical activity engagement (>8090 Kcal/week – HR: 0.70; 95% CI: 0.33, 1.49). Although results for walking and total physical activity were not statistically significant, the risk estimates were in opposite directions. A second example involves the primary study reported by Podewils et al.²⁸² While Weih et al.⁶² relied the risk estimate for the highest quartile of energy expenditure (>1657 kcal/week - RR: 0.70; 95% CI: 0.44, 1.13), other reviews^{63,267} extracted statistically significant results corresponding to the

highest frequency of activity engagement (≥ 4 activities – RR: 0.55; 95% CI: 0.34, 0.88). These examples indicate that reviews relying on the same primary studies may not necessarily arrive at the same conclusion as a result of differential data extraction.⁹⁰

Despite the various limitations, the available evidence was suggestive of a reduced risk of AD associated with higher levels of physical activity. However, further research, using objective measures and standardized definitions of physical activity levels are required to ascertain the most beneficial form, quantity, and timing (i.e. midlife, late-life) of physical activity for prevention of AD and other cognitive outcomes.^{267,272} Lastly, it is important to note that if the observed association between the variables is attributed to cognitive reserve, regular participation in physical activity may delay the onset of clinical symptoms rather than prevent the disease.^{220,228,249}

Table 19 – Physical activity and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies^a	Results	Conclusion
Podewils ²⁷⁰ (2003)	Amstar Score: 7 Publication Bias Assessed: Yes, Funnel plot, Presence of publication bias	To examine the effect of physical activities on the risk of all-cause dementia, vascular dementia, and AD.	All years up to 2002	1. Medline 2. Cinahl 3. PsycINFO	11	2 of 12	1. Cohort studies (n=7): (RR: 0.59; 95% CI: 0.42, 0.77) 2. Case-control studies (n=4): (OR: 0.24; 95% CI: 0.09, 0.60)	Physical activity was associated with a reduced risk of AD.
Weih et al. ⁶² (2007)	Amstar Score: 6 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD.	January 1966 to June 2006	1. Medline 2. Embase 3. Cochrane Database 4. Current Contents	7	5 of 12	Six of seven included studies reported risk estimates below 1.00. Results reached statistical significance in two of the six studies.	Physical activity was associated with a reduced risk of AD.

Patterson et al. ⁶³ (2007)	Amstar Score: 4 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD and other cognitive outcomes.	1966 to December 2005	1. Medline 2. Embase	2	2 of 12	Two studies detected a reduced risk of AD associated with regular or high levels of physical activity.	Physical activity was associated with a reduced risk of dementia.
Rolland et al. ²⁷² (2008)	Amstar Score: 4 Publication Bias Assessed: No	To investigate the effect of physical activity in the prevention of AD and other cognitive outcomes.	All years up to October 2007	1. PubMed 2. Medline 3. BIOSIS	10	6 of 12	Seven of ten studies (examining AD) reported a reduced risk of AD associated with physical activity (or at least one measure of physical activity).	Physical activity was associated with a reduced risk of AD/dementia.
Hamer et al. ²⁶⁶ (2008)	Amstar Score: 6 Publication Bias Assessed: Yes, Begg's asymmetry test, No evidence of publication bias ($p > 0.10$).	To examine the association between physical activity and dementia, AD, Parkinson's disease, and cognitive decline.	1990-2007	1. Medline 2. Cochrane Database of Systematic Reviews 3. Web of Science	6	5 of 12	All studies (n=6): (RR: 0.55; 95% CI: 0.36, 0.84; Test for heterogeneity: $\chi^2 = 29.12$, $p < 0.001$)	Physical activity was associated with a reduced risk of AD.
Stern et al. ²⁶⁷ (2009)	Amstar Score: 6 Publication Bias Assessed: No	To examine the effect of physical leisure activities on the risk of all-cause dementia and AD.	All years up to October 2008	1. Medline 2. Embase 3. Cinahl 4. Pubmed 5. PsycINFO 6. Cochrane CENTRAL 7. EBM Reviews 8. ISI	13	7 of 12	1. Midlife activities: Three of four studies detected a protective effect associated with physical leisure activity engagement in midlife against development of AD. 2. Late-life	Available evidence did not consistently support a protective association between physical leisure activities and AD and all-cause dementia.

				Current Contents Connect 9. ERIC 10. Austhealth 11. Health Source: Nursing/ Academic 12. Scopus 13. ProQuest Dissertation and Theses 14. Index to Theses 15. NDLTD 17. Theses Canada			activities: Six of nine studies reported an association between exposure to physical leisure activities in late-life and risk of AD.	
Lee et al. ⁶⁴ (2010)	Amstar Score: 4 Publication Bias Assessed: No	To examine the effect of several factors, including physical activity, on the risk of developing AD and other cognitive impairments.	All years up to August 2008	1. Pubmed 2. Embase 3. PsychInfo	6	4 of 12	Four of six studies detected a statistically significant reduced risk of AD associated with physical activity.	Participation in physical activities was associated with a reduced risk of AD and dementia.
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of	To examine the effect of several factors, including physical activity, on the risk of developing AD.	1984- October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	12	Referent	9 of 12 identified studies included in pooled analysis: (HR: 0.72; 95% CI: 0.53, 0.98; Test for heterogeneity: Q = 23.25, p = 0.003, I ² =	Physical activity was associated with a reduced risk of AD.

	physical activity						66%).	
Weih et al. ²⁷³ (2010)	Amstar Score: 5 Publication Bias Assessed: Yes, Funnel plot, Results not reported	To examine the effect of physical activity on the risk of developing AD.	1966-2009	1. Medline	6	5 of 12	All studies (n=6): (RR: 0.59; 95% CI: 0.50, 0.69; Test for heterogeneity: $\chi^2 = 1.84$, df = 5, p = 0.87)	Physical activity was associated with a reduced risk of AD.

^a"Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent". Item adopted from White *et al.*⁵¹

3.15 Social Engagement

Social engagement is a constituent of an “enriched environment”.^{247,248} As previously discussed, exposure to such environments can increase cognitive reserve and is therefore believed to delay the onset of clinical symptoms.^{247,248} An enriched environment, which includes “enhanced...social interactions”, may also affect the disease process.^{250,297} Two moderate^{20,62}-and one low²⁵¹-quality systematic reviews, which examined the association between social engagement and risk of AD, were identified. Evidence from five primary studies^{298,299,300,301,302} were summarized across the two moderate quality reviews.

a) Study: Weih et al.⁶²

Year: 2007

AMSTAR score: 6

Six studies were identified and included the “cognitive stimulation, leisure activities, and social contacts” section of the review reported by Weih et al. Only one³⁰² of the six studies included by Weih et al.⁶² specifically examined the effect of social engagement. The remaining studies either did not examine social engagement or considered it as a component of a composite exposure variable²⁵³ (i.e. engagement in cognitive leisure activities). The five studies reporting on the effect of cognitive leisure activities on AD incidence have been previously discussed (section 3.13).

The only included study, which reported on social engagement, observed 126 cases of AD (N = 1203) during three years of follow-up. The study detected an increased risk of AD associated with poor social networks (RR reported in review inaccurate. Correct risk estimates reported in section b). Despite the very limited evidence (i.e. offered by a single primary study), the reviewers concluded that maintaining social contacts appeared to be associated with a protective effect against the development of AD.⁶²

b) Study: Williams et al.²⁰

Year: 2010

AMSTAR score: 7

Five^{298,299,300,301,302} cohort studies, which examined the association between social engagement and risk of AD, were included in the Health Technology Assessment (HTA) reported by Wilson et al.²⁰ The studies observed an aggregate of 524 cases of AD (N=10794) over a period of follow-up ranging from 3.3 to 21 years. Studies were heterogeneous with respect to the independent variable under examination.²⁰ Two studies^{298,300} solely examined the effect of marital status, one study³⁰² examined several social network variables including “marital status, living arrangement, contact with children, satisfaction with contacts, and close social ties”, one study³⁰¹ used a global measure of social engagement according to “marital status, living arrangement, participation in social, political, or community groups, participation in social events with coworkers, and existence of a confidant relationship”, and the final study²⁹⁹ examined the effect of loneliness and social isolation.²⁰ Exposure status was ascertained according to self-report.²⁰ AD was diagnosed according to NINCDS-ADRDA or DSM criteria.²⁰

Two of three studies reported an association between marital status and risk of AD. One²⁹⁸ reported an increased risk of AD associated with never being married (RR: 2.31; 95% CI: 1.14, 4.68). Widowed and divorced subjects were not at an increased risk of AD (*Widowed* - RR: 0.82; 95% CI: 0.46, 1.44. *Divorced* - RR: 0.93; 95% CI: 0.26, 3.31). Another study³⁰² reported an increased risk of AD among single participants who lived alone when contrasted to married subjects who reported living with someone (RR: 1.90; 95% CI: 1.20, 3.10). According to the same study, married participants who lived alone were not at an increased risk of AD (RR: 1.50; 95% CI: 0.40, 6.40). The third study³⁰⁰ reported that being widowed (RR: 2.52; 95% CI: 0.80, 7.70), divorced (RR: 1.78; 95% CI: 0.70, 4.90), or single (RR: 2.06; 95% CI: 0.90, 4.70) at mid-life did not increase risk of AD.

Three studies reported on the effect of low social engagement in late-life, poor social networks and self-reported inadequate social contact with children, or loneliness. All of these variables were associated with an increased risk of AD (*Low social engagement*³⁰¹ - HR: 2.34; 95% CI: 1.18, 4.65. *Decreasing social engagement over the lifespan*³⁰¹ - HR: 1.87; 95% CI: 1.12, 3.13. *Poor social networks*³⁰² - RR: 1.60; 95% CI: 1.20, 2.10. *Inadequate social contact with children*³⁰² - RR: 2.00; 95% CI: 1.20, 3.40. *Per unit increase in loneliness*²⁹⁹ - RR: 1.51; 95% CI: 1.06, 2.14).

Based on the identified evidence, the reviewers concluded that low social engagement, loneliness, never being married and being single and living alone were associated with an increased risk of AD.²⁰

Discussion

Two moderate-quality systematic reviews concluded that high social engagement and maintaining social contacts was associated with a reduced risk of AD.^{20,62} The identified reviews were limited by the small number of available studies and heterogeneity across studies with respect to the exposures under examination. There was little overlap of primary studies across reviews. The review reported by Weih et al.⁶² contained only one³⁰² of five studies included in the referent review²⁰. Three^{298,301,302} of the five studies contained in the referent review²⁰ were published before June 2006 and were available for inclusion by Weih et al.⁶² However, only one³⁰² was included. As both reviews employed relatively similar eligibility criteria (e.g. longitudinal cohort studies reporting on AD with subjects recruited from general populations), we would expect greater overlap across reviews. As the eligibility criteria were similar across reviews, there may be alternate explanations for the non-inclusion of these studies. One such explanation may involve differences with respect to the search strategies. Although Weih et al.⁶² searched more electronic databases (four versus two) and searched across a wider range of years (1966-June 2006 vs. 1984-October 2009), fewer studies were identified as compared to the referent. A comparison of the search strings uncovers a potential explanation. Unlike the referent²⁰, Weih et al.⁶² failed to incorporate risk factor-specific search terms (e.g. “social isolation, social environment, social network, social engagement, marital status”²⁰). Rather, the reviewers relied on the term “risk factor” as a means to identify studies reporting on all life-style risk factors for AD. Differences across reviews with respect to the screening procedure may also serve as an explanation. The referent review explicitly stated that two, independent reviewers were responsible for assessing the eligibility of studies.²⁰ Weih et al.⁶² did not report the use of a similar process. As such, it is possible that study selection bias, arising from reliance on a single reviewer, may have contributed to the non-inclusion of relevant studies.

Overall, there is preliminary evidence to suggest an association between high social engagement and a reduced risk of AD. In light of the small number of available, the available evidence must be interpreted with caution. Further, the observed association may be explained by sources of bias. Importantly, the potential for reverse causation must be considered.²⁰ That is, social

disengagement may be a result, rather than a cause, of AD.²⁰ Secondly, selection bias may explain the observed association as subjects who participated in the studies may have differed from those who did not with respect to other factors associated with AD.^{94,95}

Table 20 – Social engagement and risk of AD

Study (Year)	1. AMSTAR score 2. Publication Bias Assessed (Yes/No), Test for Publication Bias, Result of test:	Objective	Years included in Search Strategy	Databases Searched	Included primary studies	Overlapping studies^a	Results	Conclusion
Weih et al. ⁶² (2007)	Amstar Score: 6 Publication Bias Assessed: No	To investigate the effect of several putative risk factors on the development of AD.	January 1966 to June 2006	1. Medline 2. Embase 3. Cochrane Database 4. Current Contents	1	1 of 5	Only one study specifically reported on the effect of social engagement on risk of AD. The study reported an increased risk of AD associated with poor social networks.	Maintaining social contacts appeared to be associated with a reduced risk of AD.
Williams et al. ²⁰ (2010)	Amstar Score: 7 Publication Bias Assessed: Not applicable for analysis of social engagement	To examine the effect of several factors on the risk of developing AD.	1984-October 27, 2009	1. Medline 2. Cochrane Database of Systematic Reviews	5	Referent	Five studies were identified. Low social engagement, poor social networks, loneliness, never being married, being single and living alone, as well as widowhood and divorce in late-life were associated with an increased risk of AD.	Poor social engagement may be associated with an increased risk of AD.

^a "Number of overlapping studies using the most recent systematic review [with the highest number of included studies] as the referent". Item adopted from White et al.⁵¹

CHAPTER 4: MEDITERRANEAN DIET ADHERENCE AND ALZHEIMER'S DISEASE: AN UPDATED SYSTEMATIC REVIEW

4.1 Background

Research suggests that adherence to the Mediterranean dietary pattern is protective against mortality and the development of cardiovascular and neurodegenerative conditions.²⁰⁹ This dietary pattern is composed of a number of components including: (1) high intake of legumes, cereals, fruits, vegetables, and fish, (2) low intake of meat and dairy products, (3) moderate intake of alcohol, and (4) a high mono-unsaturated fatty acid to saturated fatty acid ratio.²⁰⁸ Examining the effect of dietary patterns rather than individual food items or nutrients is advantageous as it takes potentially “synergistic or antagonistic” effects of nutrients into account.¹⁹⁵ Studies examining the effect of individual dietary components on risk of AD have often failed to detect an association or have yielded conflicting findings.²⁰⁷ This is relatively consistent with studies examining the putative beneficial effect of isolated nutrients on other outcomes and is likely attributed to the concept of food synergy.¹⁹⁵ That is, nutrients are likely to affect health outcomes in combination through numerous and complex biological mechanisms rather than individually.^{195,207} Furthermore, because food items or nutrients are not consumed independently, dietary patterns better reflect the reality of human food consumption.^{95,303}

Several biological mechanisms have been proposed to explain the putative association between the Mediterranean diet and risk of AD. These pathways involve several factors implicated in AD pathophysiology, namely, oxidative stress, inflammation, vascular factors, and metabolic abnormalities.^{304,305,306,318} The antioxidant and vitamin rich properties of the Mediterranean diet constituents are believed to mitigate free radical damage, afford neuroprotection, and prevent or minimize oxidative stress.^{305,306} Research has shown that foods typical of the Mediterranean diet are linked with a decrease in free radical biomarkers.³⁰⁷ Evidence suggests that omega-3 fatty acids prevent neuroinflammation, a process closely linked with oxidative stress and AD etiology.^{308,309,310} Compounds acquired from extra-virgin olive oil exhibit anti-inflammatory properties demonstrated in reductions of pro-inflammatory cytokines.³⁰⁷ Further, there is some evidence to suggest that adherence to the Mediterranean diet is associated with higher serum levels of adiponectin, an anti-inflammatory hormone.³¹¹ Although the effect of adiponectin on AD etiology remains unclear, recent studies have suggested that adiponectin is “protective against A β neurotoxicity” and that decreased serum adiponectin may be linked to cognitive impairment.^{312,313} Although one³¹⁴ study

detected a reduced risk of mild cognitive impairment associated with an increase in plasma adiponectin, conflicting evidence is also available suggesting that elevated adiponectin may be associated with a detrimental effect with respect to dementia and AD³¹⁵. Finally, it has been hypothesized that the beneficial effect of the Mediterranean diet against AD may be afforded by the diet's ability to prevent putative AD risk factors, namely, "vascular co-morbidities, dyslipidemia, hypertension, and coronary artery disease."³⁰⁷

4.2 Objective

The objective of the study is to provide an up-to-date systematic review regarding the association between Mediterranean diet adherence and risk of AD. As several existing reviews reporting on the Mediterranean diet were available (Section 3.9), one of which was deemed to be of high methodological quality, a *de novo* systematic review was unwarranted. The systematic review reported by Sofi et al.²⁰⁹ was eligible for an update as it adhered to all of the *a priori* established criteria required for an update (Section 2.2): (1) the review was deemed to be of high methodological quality according to the AMSTAR instrument, (2) duplicate screening and data extraction were employed, and (3) identified studies were quality appraised. As reported by Moher et al., an updated systematic review adheres to the protocol of the original review.⁴⁵ Sofi et al.²⁰⁹ considered a number of health outcomes including, but not limited to, AD. Although the updated review largely adhered to the methodology reported by Sofi et al.²⁰⁹, some alterations were deemed necessary to limit the review to AD.

4.3 Literature search strategy

To identify studies reporting on Mediterranean diet adherence and risk of AD, we adapted the search strategy reported by Sofi et al.²⁰⁹ As we were solely interested in studies reporting on AD, we excluded search terms for other outcomes (e.g. cardiovascular disease, neoplasm, neoplastic disease, Parkinson's disease, etc.) considered by the original reviewers. All databases searched by Sofi et al.²⁰⁹ were re-searched to identify studies published after the review, allowing for a one year overlap to address the "lagtime between publication of an article and its inclusion into standardized literature retrieval databases".⁵¹ These databases included: MEDLINE, EMBASE, Web of Science, The Cochrane Library (The Cochrane Central Register of Controlled Trials), clinicaltrials.org, and Google Scholar. Additional electronic databases (PsycINFO, CINAHL, and AARP Ageline) were also considered as a means to further expand the search. The search strategy involved exposure,

outcome, and study design terminology. Using the MEDLINE search as an example, exposure terminology included “Mediterranean diet.mp”, “Diet, Mediterranean/”, “Mediterranean.mp”, “diet/”, “diet.mp”, “food habits/”, “dietary pattern.mp”, “adherence.mp”, and “score.mp.”. Outcome terminology included “Alzheimer disease/”, “dementia/”, “Alzheimer*.mp”, “presenile dementia*.mp”, “acute confusional senile dementia.mp”, “Senile dementia*.mp”, “primary senile degenerative dementia.mp”, “primary degenerative senile.mp”. Study design terminology included “prospective.mp”, “prospective studies/”, “follow-up studies/”, “follow-up.mp”, “Cohort Studies/”, “cohort.mp”. In alternate databases, the search strategy retained its structure; however, database-specific medical subject headings were applied to ensure compatibility. Year limits were applied (2009 to Sept. 2013) to identify studies published after the original review while allowing for a one-year overlap.⁵¹ The grey literature search involved a handsearch of two disease-specific journals, namely the *International Journal of Alzheimer’s disease* and the *American Journal of Alzheimer’s disease and Other Dementias*, an internet search of Google and GoogleScholar, and a search for dissertations and theses (ProQuest Dissertation and Theses). A search of the grey literature was conducted in October 2013. Refer to Appendix C-1 for the grey literature and database specific search strategies.

4.4 Selection Criteria

A two-tiered screening approach was employed. Following a review of the title and abstract, the full text of relevant and potentially relevant studies were scrutinized according to the eligibility criteria proposed by Sofi et al.²⁰⁹ More specifically, Sofi et al. considered “studies that prospectively evaluated the association of an a priori score used for assessing adherence to the Mediterranean diet and adverse clinical outcomes.”²⁰⁹ These criteria were adapted to satisfy the objective of the present study. Studies were eligible for inclusion if (1) the study design was prospective, (2) a scoring system was in place for estimating exposure, and (3) the study reported on AD. To remain consistent with the protocol of the original review, the following exclusion criteria were adopted: “studies [with]... a cross-sectional or case-control design, [those that] analyzed adherence to a nonspecific dietary pattern or a recommended dietary guideline and not to the Mediterranean diet, [those that] evaluated cohort of patients who suffered from a prior clinical event (i.e., in a secondary prevention), [those that] did not adjust or potential confounders, and [those that] did not report an adequate statistical analysis”.²⁰⁹ Research has suggested that data summarized in conference abstracts frequently differs from results presented in the full published report.³¹⁶ Following research recommendations, authors of conference abstracts were contacted as a means to obtain the full

report.³¹⁶ When the full report could not be retrieved, conference abstracts were excluded. Studies identified and included in the previous reviews reported by Sofi et al.^{208,209} were also excluded as this data was summarized elsewhere (Section 3.9). Finally, commentaries or editorials lacking primary data were also excluded.

Studies satisfying the following criteria were eligible for inclusion:

- **Population** – Humans
- **Exposure** – Mediterranean diet estimated according to an a priori established scoring system²⁰⁹
- **Outcome**– Diagnosis of Alzheimer’s disease
- **Study Design** –Prospective studies

Studies were excluded from the review if any of the following criteria were satisfied:

- The outcome of interest was cognitive decline, mild cognitive impairment (MCI) or non-AD dementias (ex. Frontotemporal dementia, Pick’s disease, Lewy body dementia, Vascular dementia, Creutzfeldt-Jakob disease)
- The study failed to distinguish AD from all-cause dementia or dementia subtypes (e.g. study reported on risk of all-cause dementia and did not provide risk estimates for Alzheimer’s disease)
- The study was focused on progression from MCI to AD (i.e. study examines cognitively impaired subjects)
- The study examined a “nonspecific dietary pattern or a recommended dietary guideline and not to the Mediterranean diet”²⁰⁹
- The study employed an alternative methodological design (e.g. cross-sectional studies, case-control studies, systematic reviews, narrative reviews, etc.)²⁰⁹
- The study “evaluated cohort of patients who suffered from a prior clinical event (i.e., in a secondary prevention)”²⁰⁹
- The study “did not adjust or potential confounders [or] did not report an adequate statistical analysis”²⁰⁹
- The study was included in original reviews by Sofi et al.^{208,209}
- Commentary or editorial with no primary data
- Full-text of the article could not be obtained

4.5 Study Selection Method

To minimize the biased inclusion of studies and to adhere to the protocol of the original study, all identified studies were independently screened by two reviewers. In the event of discordance, the study in question was re-examined by both reviewers and a decision was reached through consensus. Studies that satisfied the selection criteria advanced to the quality assessment phase of the review.

4.6 Quality Appraisal

Sofi et al. considered three criteria to estimate study quality: sample size, length of follow-up, and rigour of confounding adjustment.²⁰⁹ To remain consistent with the protocol of the original review, these criteria were also considered in the quality appraisal process. As described by Sofi et al. “studies with a high number of participants, long duration of follow-up, and adjustment for confounders that include demographic, anthropometric, and traditional risk factors were considered of high quality”.²⁰⁹ As this quality appraisal method is relatively vague, more specific guidelines were developed for each criterion. Ensuring that a sufficient number of subjects are enrolled to detect statistical significance is integral and should be considered in the quality appraisal of primary studies.²⁰ Thus, studies that described a power calculation to arrive at a sufficient sample size were considered superior with respect to the first quality appraisal criterion.²⁰ To remain consistent with AD research, adequate length of follow-up was defined as a minimum of two years.²⁰ For the third and final criterion, studies were required to control for the potentially confounding effect of demographic, lifestyle, and comorbid factors. Quality assessment was conducted independently by two reviews.

4.7 Data Extraction Strategy

To minimize the potential for bias, data was independently extracted by two reviewers. In the event of discordant data collection, concordance was attained through discussion. In keeping with the original review, the following variables were extracted: “lead author, year of publication, cohort name, country of origin of the cohort, sample size of the cohort, ...duration of follow-up, age at entry, sex, ...components of the Mediterranean diet adherence score, and variables that entered into the multivariable model as potential confounders”.²⁰⁹ As the update was specific to a single

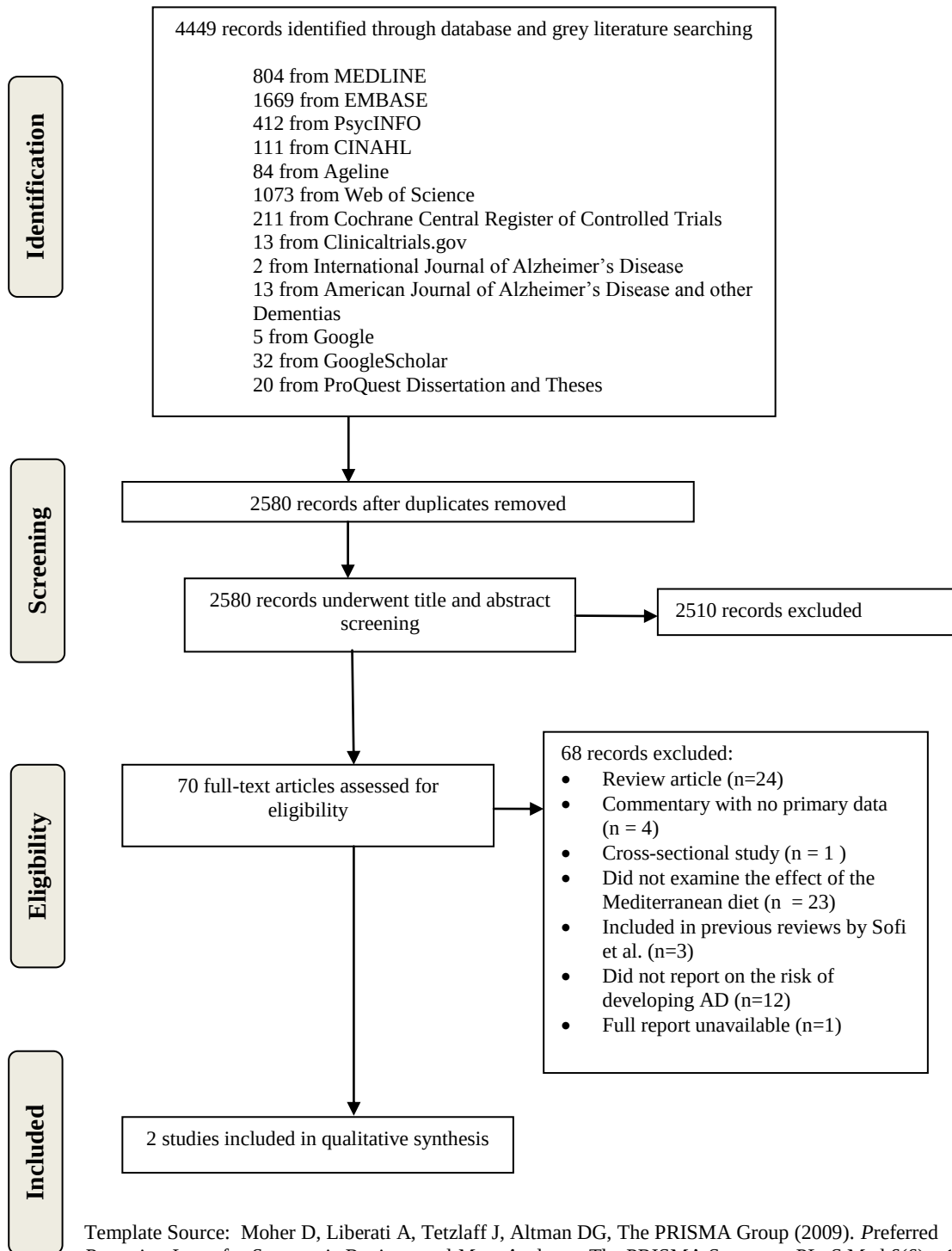
outcome, “outcome”, and “number of outcomes”, which were items considered by the original reviewers, were deemed irrelevant and excluded.

4.8 Literature Search Results

The database search yielded 4449 articles. Of these studies, 804 citations were retrieved from MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations databases, 1669 from EMBASE and EMBASE Classic, 111 from CINAHL, 412 from PsycINFO, and 84 from AgeLine, 1073 from Web of Science, 211 from the Cochrane Central Register of Controlled Trials, and 13 from clinicaltrials.gov. An additional 72 records were identified through the grey literature search. A total of 2580 unique records remained following the duplicate citation removal process. Of the 2580 studies, 2510 were deemed irrelevant based on a review of the title and abstract and were consequently excluded.

Of the remaining 70 studies eligible for full article screening, one conference proceeding³¹⁷ was excluded as the full report was unavailable and could not be obtained from the authors. Sixty-seven studies were deemed irrelevant following full text review. Of these, 24 were reviews, four were commentaries lacking primary data, one was a cross-sectional study, 12 did not report on the risk of developing AD, 23 did not examine the effect of the Mediterranean diet (i.e. examined a non-specific dietary pattern, single nutrient, or an entirely irrelevant exposure such as cognitive stimulation), and three were already included in previous reviews reported by Sofi et al.^{208,209} Refer to Figure 3 for the flow of studies at each stage of the review process. A list of the 68 studies excluded in the secondary screening phase, along with reasons for exclusion, can be found in Appendix B-2.

Figure 3 - PRISMA Flow Diagram: Updated Systematic Review



Template Source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

4.9 Clinical and methodological characteristics

Both^{211,318} included studies examined the same cohort of subjects. Participants were enrolled in the Washington Heights-Inwood Columbia Aging Project II (WHICAP II), a prospective community-based study which examined participants enrolled in the original WHICAP cohorts recruited in 1992 and 1999.^{211,318} Briefly, participants were elderly (≥ 65 years) Medicare recipients residing in northern Manhattan selected through random sampling.³¹⁹ The sample was multi-ethnic with approximately equal proportions of White, Black, and Hispanic study participants.^{211,318,319} Mean age at baseline reported in both studies was approximately 77.0 years and over 65% of participants were female.

The mean length of follow-up was slightly longer in the study reported by Scarmeas et al.²¹¹ (3.8 vs. 5.4 years). According to the report by Scarmeas et al.²¹¹, follow-up data was available for 85% of all eligible subjects, namely, those with both dietary and physical activity data (n=2247). Of the 339 subjects with no follow-up data, 270 were lost to follow-up while 69 died within a year and a half of study initiation. There was a statistically significant difference between those with and without follow-up data with respect to age, caloric intake, BMI, number of co-morbidities, and cognitive performance. More specifically, those with follow-up data were older and were generally healthier with respect to the examined variables (lower caloric intake and BMI, less co-morbidities, better cognitive functioning).²¹¹

Follow-up data was missing for 19.4% of the 2778 participants considered for inclusion by Gu et al.³¹⁸ An additional 1021 subjects were also excluded due to prevalent dementia, unavailability of frozen blood samples for biomarker analysis, lack of data to adequately ascertain Mediterranean diet adherence, and development of non-AD dementia.³¹⁸ Excluded subjects differed significantly from included subjects with respect to age, education, co-morbidities, race, smoking and APOE e4 status. Those excluded had a greater likelihood of being Black or Hispanic, older, less educated, APOE e4 carriers, and non-smokers.³¹⁸ Excluded subjects also had a greater number of comorbidities.³¹⁸ The characteristics and findings of the identified studies are summarized in Table 21.

4.10 Exposure ascertainment

Adherence to the Mediterranean diet was assessed in the same manner in both studies. Dietary intake was ascertained according to a semi-quantitative food frequency questionnaire (FFQ), namely, the Willet 61-item FFQ. The questionnaire demonstrated validity and reliability in elderly

subjects and specifically in WHICAP participants.³¹⁸ The self-administered FFQ required subjects to recall the average frequency of consumption of 126 foods over the past year.³²⁰ To assign an adherence score for each subject, consumption of certain foods was compared to the sex-specific population median. High intake defined as consumption above the median.^{209,318} Those with a high intake of legumes, fruits, vegetables, cereals, and fish were assigned a score of one for each item.^{209,318} Those consuming quantities less than the established threshold were assigned a score of zero. Conversely, those with a high intake of foods atypical of the Mediterranean diet, such as meats and dairy, were assigned a score of zero.^{209,318} Those with a low intake were given a score of one. Mild to moderate alcohol consumption (>0 to <30 g/d) and a high monounsaturated fats to saturated fats ratio also warranted a point each.^{209,318} A single combined score was derived with a maximum possible score of 9 indicating highest adherence.²⁰⁹ In categorical analyses, low, moderate, and high adherence were defined as scores ranging from 0 to 3, 4 to 5, and 6 to 9, respectively.^{209,318}

4.11 Outcome ascertainment

According to both publications, prevalent cases of dementia and/or AD were excluded at baseline.^{211,318} AD was ascertained according to a diagnostic work-up involving neurological examination, medical history, physical examination, cognitive function testing, and in-person interviews.^{211,318} When available, brain imaging data was also considered.^{211,318} AD was then ascertained according to the NINCDS-ADRDA by a consensus panel of neurologists and neuropsychologists.^{211,318}

4.12 Covariates

Multivariable-adjusted Cox proportional hazards models were used in both studies to estimate hazard ratios (HRs) and 95% CIs. Both studies reported analyses adjusted for age, education, caloric intake, BMI, gender, smoking status, ethnicity, APOE genotype, and medical co-morbidities (“myocardial infarction, congestive heart failure, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, arthritis, gastrointestinal tract disease, mild liver disease, diabetes, chronic renal disease, and systemic malignancy”²¹¹). The report by Scarmeas et al.²¹¹ also considered cohort (1992 vs. 1999 recruitment), depression, leisure activities, duration between first dietary and physical activity assessment, and baseline Clinical Dementia Rating (CDR) score, which measures severity of AD³²¹, as covariates. To examine whether the association between Mediterranean diet adherence and risk of AD was explained by inflammatory and metabolic

mechanisms, Gu et al.³¹⁸ provided risk estimates adjusted for high sensitivity C-reactive protein (hsCRP), fasting insulin, and adiponectin.

4.13 Quality appraisal

Sample size, length of follow-up and rigour of confounding adjustment were considered for the purpose of quality appraisal.²⁰⁹ While Scarmeas et al.²¹¹ described a power calculation to arrive at a sufficient sample size, Gu et al.³¹⁸ provided no such information. Both studies reported follow-up durations exceeding two years. Finally, as previously described, both studies employed extensive confounding adjustment. According to the criteria proposed by Sofi et al.²⁰⁹, both identified studies were of moderate to high methodological quality.

4.14 Statistical Analysis

The small number of identified studies precluded a meta-analysis. Furthermore, three^{207,211,318} of the four available studies (two identified in the present review and one identified in previous reviews reported by Sofi et al.²⁰⁸) examined the same cohort of subjects. Consequently, de novo and updated pooled analyses were not conducted in an effort to avoid double-counting subjects.³²²

Table 21 - Characteristics and findings of the included studies

Author, year (cohort)	Country, Study population	Sample size (cases/total n)	Components of the adherence score	Method of AD ascertainment	Length of follow-up, mean (SD)	Age at baseline, mean (SD); Gender (% female)	Covariates	Results, Risk estimate: (95% CI)
Gu et al., 2009 ³¹⁸ (WHICAP II)	United States, Medicare recipients ≥65 years of age residing in Manhattan; participants were recruited from two WHICAP cohorts recruited in 1992 and 1999	118/1219	1. High intake of legumes, fruits, vegetables, cereals, fish 2. Low intake of meat and dairy products 3. High monounsaturated fats to saturated fats ratio 4. Mild to moderate alcohol consumption (>0 to <30 g/d)	NINCDS-ADRDA	3.8 (1.3)	76.7 (6.4); 66.6%	Age, education, caloric intake, BMI, gender, smoking status, ethnicity, APOE genotype, comorbidity index, hsCRP, fasting insulin, adiponectin	Minimally adjusted analysis: Treated continuously – HR: 0.87 (0.78, 0.97); p = 0.01 Middle vs. lowest tertile – HR: 0.57 (0.37, 0.88); p = 0.01 Highest vs. lowest tertile – HR: 0.66 (0.41, 1.04); p = 0.08; p for trend = 0.04 Analysis adjusted for additional variables (excluding biomarkers): Highest vs. lowest tertile: HR: 0.66

								(0.41, 1.06); p for trend = 0.06 Analysis adjusted for demographic variables and biomarkers (includes n= 1202 with biomarker data): Continuous variable – HR: 0.87 (0.78, 0.97); p = 0.01 Middle vs. lowest tertile – HR: 0.56 (0.36, 0.86); p = 0.01 Highest vs. lowest tertile - HR: 0.68 (0.42, 1.08); p = 0.10; p for trend = 0.06
Scarmeas et al., 2009 ²¹¹ (WHICAP II)	United States, Medicare recipients ≥65 years of age residing in Manhattan; participants were recruited from two WHICAP cohorts recruited	282/1880	1. High intake of legumes, fruits, vegetables, cereals, fish 2. Low intake of meat and dairy products 3. High monounsaturated fats to saturated fats ratio	NINCDS - ADRDA	5.4 (3.3)	77.2 (6.6); 68.8%	Age, education, caloric intake, BMI, cohort (1992 vs. 1999), sex, APOE genotype, smoking status, depression, leisure	Mediterranean diet (when considered in the same model as physical activity): Medium vs. lowest tertile – HR: 0.98 (0.72, 1.33); p = 0.88 Highest vs. lowest tertile - HR: 0.60 (0.42, 0.87); p = 0.007; p for trend = 0.008

	in 1992 and 1999		4. Mild to moderate alcohol consumption (>0 to <30 g/d)				activities, ethnicity, comorbidity index, baseline Clinical Dementia Rating score, time between first dietary and first physical activity assessment	

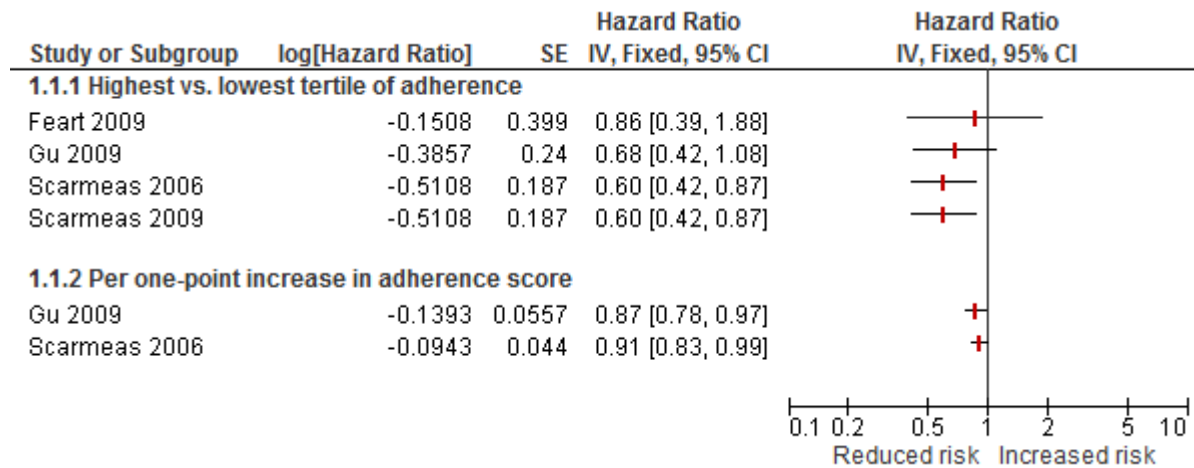
Table adapted from Sofi et al.²⁰⁹

4.15 Study findings

Of the 1219 subjects followed by Gu et al., 118 developed incident AD.³¹⁸ According to the minimally adjusted model (age, gender, education, race) with Mediterranean diet treated as a continuous variable, higher adherence was associated with a reduced risk of AD (HR: 0.87; 95% CI: 0.78, 0.97; $p = 0.01$). When compliance to the dietary pattern was treated categorically, moderate and high adherers had a 43% and 34% reduced risk of AD, respectively, with a statistically significant p -value for trend (*Moderate* – HR: 0.57; 95% CI: 0.37, 0.88. *High* – HR: 0.66; 95% CI: 0.41, 1.04; p -value for trend = 0.04). The highest tertile of adherence did not reach statistical significance, however. The trend test was marginally significant according to the analysis adjusted for additional covariates, namely, caloric intake, BMI, smoking status, APOE genotype, and medical co-morbidities ($p = 0.06$). To examine whether the association between the Mediterranean diet and risk of AD could be explained by inflammatory and metabolic mechanisms, analyses were repeated with additional covariate adjustments for inflammatory (high-sensitivity C-reactive protein (hsCRP)) and metabolic (fasting insulin, adiponectin) biomarkers.³¹⁸ Biomarker data was available for 1202 subjects. According to the analysis adjusted for age, gender, education, race, hsCRP, fasting insulin and adiponectin, each point increase in the Mediterranean diet adherence score (0 to 9) was associated with a significant reduced risk of AD (HR: 0.87; 95% CI: 0.78, 0.97; $p = 0.01$). Considered categorically, both moderate and high adherence yielded risk estimates below 1.00. However, only the moderate adherence category reached statistical significance (*Moderate* – HR: 0.56; 95% CI: 0.36, 0.86. *High* – HR: 0.68; 95% CI: 0.42, 1.08; p -value for trend = 0.06). According to the authors, the lack of change in the risk estimates upon adjustments for inflammatory and metabolic biomarkers was indicative that alternate biological mechanisms may explain the association between Mediterranean diet adherence and risk of AD.³¹⁸

Scarmeas et al.²¹¹ examined the effect of physical activity and adherence to the Mediterranean diet on risk of developing AD. A total of 1880 subjects, 282 of whom developed incident dementia during follow-up, were eligible for inclusion in the analyses. When introduced into the same model, engaging in physical activity and adherence to the Mediterranean diet were both inversely associated with risk of AD.²¹¹ While moderate adherence was not associated with a significant decrease AD risk, high adherence was associated with a statistically significant 40% reduction in risk (*Moderate* – HR: 0.98; 95% CI: 0.72, 1.33. *High* – HR: 0.60; 95% CI: 0.42, 0.87).

Figure 4 - Forest plot of available studies on Mediterranean diet adherence and risk of AD



4.16 Discussion

The present updated systematic review identified two^{211,318} publications reporting on the same cohort of subjects (WHICAP). An earlier publication²⁰⁷ identified in previous reviews by Sofi et al.^{208, 209} also reported on the WHICAP cohort. Findings from the WHICAP study^{207,211,318} suggest a statistically significant inverse association between Mediterranean diet adherence and risk of AD. One study²¹⁰ identified by Sofi et al.²⁰⁹, which examined a unique cohort of subjects, did not detect a statistically significant association between higher adherence to the Mediterranean diet and a reduced risk of AD. As described in the literature, a possible explanation for this inconsistent finding may be attributed to “dietary or cultural differences”.³²³ While the WHICAP cohort examined an ethnically diverse American population, subjects recruited in the Three-City study were residents of Bordeaux, France.²¹⁰ As hypothesized, there may be slight variations with respect to the characteristics of the Mediterranean diet across cultures.^{323,324} Moreover, other cultural disparities may also impact the effect of the Mediterranean diet on AD incidence.³²³ As noted by Feart et al., cultural differences with respect to multivitamin supplementation, that is, greater uptake of multivitamins among elderly Americans as compared to the elderly French population, is one possible explanation.²¹⁰

Results reported by Gu et al.³¹⁸ have contributed evidence towards understanding putative biological pathways linking the variables of interest. Risk estimates remained unchanged following adjustments for inflammatory and metabolic biomarkers.³¹⁸ If it is hypothesized that inflammation or metabolic dysfunction explains or “mediates” the association between the variables of interest, we would expect a change between the biomarker unadjusted and adjusted risk estimates.³²⁵ As the risk

estimates did not change following individual and concurrent biomarker adjustment, the authors concluded that the association between Mediterranean diet adherence and AD “did not seem to be mediated by hsCRP, fasting insulin, or adiponectin”.³¹⁸ The authors caution that this finding does not invalidate the hypothesized inflammatory and metabolic mechanisms as other biomarkers involved in these pathways remain unexamined.³¹⁸

Despite the prospective nature of the WHICAP study, several methodological limitations must be addressed. The study reported the use of a standardized FFQ to ascertain dietary intake. While FFQs are considered an acceptable means for measuring compliance to the Mediterranean dietary pattern, the need to recall food intake over the last 12 months introduces the potential for recall error.³²⁴ Research also suggests that reliance on self-reported measures of dietary intake may introduce exposure measurement error as unhealthy foods are often underreported while consumption of healthy foods are overreported.⁹² Reliance on FFQs is likely to underestimate the true association between the variables of interest if recall or reporting error is unassociated with the outcome of interest.^{157,318,324} Alternatively, if the ability to recall past exposures is related to the outcome of interest, other types of exposure measurement bias may arise.^{72,326} This is particularly problematic in dementia research as the disease process directly effects memory function and consequently, recall accuracy.²¹¹ While the study was prospective in nature and explicitly noted the exclusion of prevalent dementia cases at baseline, cases of predementia or mild AD may have been missed as diagnostic tools may lack the ability to detect such cases.²¹ Subjects with mild cognitive deficits were clearly included in the study reported by Scarmeas et al.²¹¹ Consequently, the potential for differential recall cannot be eliminated as cognitively impaired subjects may have been less likely to accurately recall past exposure history.²⁰⁷ Limitations associated with self-reported dietary intake has highlighted the need for nutrient biomarker analysis to corroborate self-reported data.²⁰³ Research suggests that estimation of Mediterranean diet using objective biomarkers is feasible.³²⁷ Finally, criticisms have been raised with respect to the calculation of the Mediterranean diet adherence score employed in both studies.³²⁸ The commonly used scoring process compares consumption of each dietary pattern component to the population median.^{207,208,209,211,318} Critics have suggested that the distribution of scores should instead be based on thresholds prescribed by the Mediterranean diet pyramid.³²⁸ As suggested, the proposed method would better embody “adherence to the traditional Mediterranean diet”.³²⁸

Inclusion of subjects with mild cognitive impairments or prevalent dementia at baseline may give rise to reverse causality if exposure status is altered as a result of the disease.⁹³ While Scarmeas et al. explicitly reported the inclusion of subjects with mild cognitive deficits (CDR score of 0.5), all analyses were adjusted for baseline CDR score.²¹¹ Moreover, results remained relatively unchanged

when such cases were excluded from analyses examining the combined association of physical activity and Mediterranean diet adherence with risk of developing AD.²¹¹ In a previous study of the same cohort reported by the same author²⁰⁷, results remained consistent when subjects with mild cognitive deficits at baseline were excluded from the analysis which sought to examine the independent effect of Mediterranean diet adherence. Analyses reported by Gu et al. did not control for baseline CDR score nor were sensitivity analyses excluding cognitively impaired subjects conducted.³¹⁸ Although the potential for reverse causality cannot be entirely eliminated, previous research by Scarmeas et al. found that adherence to the Mediterranean diet was likely not influenced by mild cognitive deficits.²⁰⁷ More specifically, analyses of dietary intake ascertained at multiple time points suggested that adherence scores of subjects who did and did not develop AD remained consistent over a duration of more than 7 years.²⁰⁷

Because AD can only be definitively diagnosed post-mortem according to neuropathological examination, the potential for outcome misclassification error is heightened when diagnosis relies solely on antemortem assessments.²¹ Outcome misclassification error can be reduced by ensuring that the data used to guide the diagnostic process is as accurate as possible.³²⁹ With respect to the NINCDS-ADRDA, this can be achieved by relying on experienced clinicians or personnel for the administration of the tool, incorporating objective measures (i.e. brain imaging), and further reducing subjectivity by employing a "consensus" panel decision making process.²⁶ Both included publications indicated that a physician performed the neurological assessments and that a consensus diagnostic procedure, involving a panel of neurologists and neuropsychologists, was employed.^{211,318} Scarmeas et al.²¹¹ indicated that computed tomography and magnetic resonance imaging data were used when available. The effect of the misclassification error is dependent on whether the measurement error is associated with the exposure under study.³³⁰ Gu et al.³¹⁸ explicitly reported that members of the consensus panel were unaware of adherence status. This would suggest that disease misclassification would be unrelated to exposure status and would likely attenuate the association between the variables of interest.³³⁰

Participants who enroll or remain in a study may differ, with respect to the exposure and outcome of interest, from those who refuse participation or are lost to follow-up.^{94,95} Participants who enroll in the study may engage in healthy behaviours, in addition to adhering to a Mediterranean diet, which may explain the association between the variables of interest.⁹⁵ Further, cohort studies may be susceptible to selection bias arising from differential losses to follow-up.³³¹ If losses to follow-up were associated with adherence to the Mediterranean diet and the development of AD, the derived risk estimates would be erroneously attenuated or inflated.²⁴⁵ Both publications noted a difference between those lost to follow-up or otherwise excluded from the analysis (due to missing

frozen blood samples³¹⁸, missing dietary intake assessments or physical activity data²¹¹) and those retained in the study. Gu et al. reported that “participants with loss of follow-up or lack of blood samples were different from the remaining participants with regard to some AD risk factors”.³¹⁸ Similarly, Scarmeas et al.²¹¹ noted that subjects lost to follow-up or those excluded due to missing data differed from those included in the analysis with respect to putative AD risk factors such as education, BMI and co-morbidities. While there was evidence that losses to follow-up or exclusions due to missing data were related to risk factors for the outcome of interest, this would likely give rise to biased risk estimates if losses or exclusions were also associated with Mediterranean diet adherence.²⁴⁵ According to an earlier publication examining the same cohort²⁰⁷, those excluded from analyses did not differ from those retained with respect to exposure status. Moreover, several of the putative risk factors for AD, including age, sex, education, APOE e4 status, co-morbidity index, and BMI were unassociated with adherence to the Mediterranean diet. Despite these findings, the potential for selection bias in the WHICAP study cannot be entirely eliminated.

While the observed association between adherence to the Mediterranean diet and risk of AD may be explained by confounding, both publications reported analyses adjusted for several demographic, lifestyle, and comorbid factors. Analyses were also adjusted for APOE genotype, an established risk factor for AD.³³² There is some evidence to suggest that caloric intake is associated with the Mediterranean diet²⁰⁷ and risk for Alzheimer’s disease²¹⁵. Analyses also accounted for the confounding effect of caloric intake. Despite the rigorous adjustments for potentially confounding variables, residual confounding due to unmeasured or inadequately measured variables cannot be omitted.³³³

Although this update provides some evidence of an association between Mediterranean diet adherence and risk of AD, the current evidence is inadequate for informing public health policy with respect to the development of dietary guidelines or interventions as no independent studies were identified. The small yield of this updated review is reflective of the short duration between the current review and that reported by Sofi et al.²⁰⁹ However, the time interval adheres to the Cochrane recommendation of updating reviews every two years.³³⁴ The small number of available studies coupled with important limitations of the observational study design warrant cautious interpretation of the findings. Only a single study reported in three^{207,211,318} publications is suggestive of a reduced risk of AD associated with higher adherence to the Mediterranean diet. Potential for selection bias, residual confounding, differential dietary recall and other potential sources of bias may explain the observed association. Further, all three^{207,211,318} publications examine subjects derived from the same cohort. Despite the generalizability of the ethnically diverse WHICAP cohort^{207,211,318,319}, further studies examining different populations are needed to confirm the association between adherence to

the Mediterranean diet and risk of incident AD. While RCTs may overcome a number of limitations associated with observational studies, the logistics (i.e. blinding, adherence) of conducting dietary intervention studies are complex and costly.⁹⁵ Nonetheless, intervention studies have been conducted to examine the effect of Mediterranean diet adherence on cardiovascular outcomes.²⁰⁷ Currently, the small number of available studies precludes a definitive conclusion regarding the association between Mediterranean diet adherence and risk of AD. While adherence to a healthy Mediterranean-like dietary pattern may confer health benefits, limited evidence precludes the development of dietary guidelines centered around the traditional Mediterranean diet as a primary prevention strategy for addressing AD incidence.^{95,207}

CHAPTER 5: PSYCHOLOGICAL STRESS AND ALZHEIMER'S DISEASE: A DE NOVO SYSTEMATIC REVIEW

5.1 Background

Psychological stress has been implicated as a putative risk factor for numerous diseases including depression, hypertension, cardiovascular disease, cognitive decline and Alzheimer's disease.^{335,336,337,338,339} Experimental studies have suggested that exposure to prolonged stress can expedite age-related changes.³⁴⁰ Exposure to stress initiates a series of events involving the hypothalamic-pituitary-adrenal (HPA) axis which is regulated by a negative feedback mechanism.³⁴⁰ The sequence of events is initiated by the secretion of cortisol releasing factor (CRF) from the hypothalamus which then activates the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary.^{340,341} Next, ACTH triggers the discharge of glucocorticoids from the adrenal gland.^{340,341} Glucocorticoids are integral to the stress response system as "they mobilize energy, increase cardiovascular tone, and suppress unessential anabolism such as growth, reproduction and inflammation" allowing the subject to adequately respond to the stressor.^{340,341} Moreover, glucocorticoids are essential for regulating the negative feedback mechanism by ceasing release of CRF and ACTH.^{340,341}

Although activation of the HPA-axis resulting in the release of glucocorticoids is integral for adequately responding to episodes of acute stress, chronic or prolonged periods of stress may result in "HPA-axis dysregulation" stemming from the inability of glucocorticoids to terminate the release of CRF through negative feedback.^{340,342} This impairment is due to "hypersecretion" of CRF and subsequent glucocorticoid excess.³⁴² Glucocorticoid surplus has been associated with several pathological states including "myopathy, steroid diabetes, hypertension, immunosuppression, infertility, and inhibition of growth".³⁴⁰ Experimental studies have shown that HPA-axis dysfunction resulting in excess cortisol, a glucocorticoid, leads to AD-related pathology including excess amyloid-beta plaques and tau protein.³⁴³ Excess glucocorticoid levels have also been associated with hippocampal atrophy which ultimately results in cognitive impairment and memory deficits.^{344,345} Known as the glucocorticoid cascade hypothesis, it is hypothesized that the ensuing hippocampal atrophy further impacts the HPA-axis resulting in additional hippocampal damage.^{340,344} Because hippocampal damage is characteristic of Alzheimer's disease, examining the effect of chronic stress and subsequent HPA-dysfunction may provide insight into the etiology of AD.³⁴⁴

Experimental studies have examined potential biological mechanisms linking stress and Alzheimer's disease. Studies have found that exposure to stress is associated with production and

accumulation of amyloid β (A β) and tau protein, constituents of the histopathological indicators of AD, amyloid plaques and neurofibrillary tangles.^{13,14,346,347,348} Using mouse models, Rissman et al. have demonstrated that exposure to prolonged or recurrent emotional stress resulted in increased tau phosphorylation in the hippocampus and production of insoluble tau protein.³⁴⁶ However, exposure to acute stress did not yield a sustained detrimental effect, suggesting that only chronic stress may be associated with AD pathology.³⁴⁶ The effect of stress on A β has also been examined in vivo.^{347,348} Dong et al. reported increased amyloid plaque formation in Tg2576 mice following exposure to stress.³⁴⁷ In a second study, exposure to both chronic and acute stress increased interstitial fluid (ISF) A β levels in mice.³⁴⁸ Because A β concentrations are associated with amyloid plaque formation, an integral component of AD pathophysiology responsible for neuronal damage, the effect of stress on A β concentrations is a viable mechanism by which exposure to stress may increase the risk of AD.^{14,348} Alternate biological mechanisms have also been proposed to explain the association between stress and AD. Stress has been associated with excess pro-inflammatory cytokines and subsequent neuroinflammation, a factor implicated in AD-related pathological changes.^{343,349} Secondly, stress is associated with a number of putative risk factors for AD including “cardiovascular disease, hypertension, and central adiposity”.³⁴³

Conceptualization of Stress

The complexity of the conceptualization of stress is reflected in the numerous definitions and theoretical models available. However, the different conceptualizations of stress can be synthesized into three broad categories: the engineering, physiological, and psychological approaches.^{350,351} The engineering and physiological approaches define stress as the environmental stimuli and the physiological response to external stimuli, respectively.^{350,351} The psychological approach provides a more sophisticated conceptualization of stress. According to this approach, stress is the “dynamic interaction between the individual and their environment”.³⁵¹ It takes psychological factors that impact the interaction between man and environment into consideration.^{350,351} This is considered the most thorough conceptualization of stress.³⁵⁰

The psychological approach has given rise to interactional and transactional theories.³⁵¹ Interactional theories, such as the Person-Environment Fit (PE-fit) and the Demand-Control-Support (DCS) models, focus on the “structural characteristics” of the individual-environment (i.e. work) interaction.^{350,351} In the PE-fit model, individual and environmental factors impact the “goodness of fit”.^{350,351} Optimal fit occurs when individual factors (e.g. skills and abilities) are able to satisfy work demands and in turn, the individual’s needs are met and skills and abilities utilized.^{350,351} Potential for stress is minimized under such conditions. The DCS model initially centered around job demand

and control.^{350,351} According to this model, stress and subsequent illness arises as a result of high job demand and low job control.^{350,351} Higher job control or support are believed to mitigate the effect of high job demand.³⁵⁰ An important limitation of this model involves the failure to consider “individual differences”.³⁵⁰ A cited example involves the differential need for control.³⁵⁰ That is, high control may not be universally beneficial (i.e. may cause stress in some).³⁵⁰ As noted by Broome et al., while both interactional models have been described in the context of the workplace, they can be applied to other environments.³⁵¹

Transactional theories center around perceptions of stress and therefore, “cognitive processes”.^{350,351} The Cognitive Theory of Psychological Stress and Coping is one example.³⁵⁰ Briefly, the potential stressor is evaluated and if necessary, coping mechanisms are implemented.³⁵⁰ This theory integrates the concept of individual differences as such factors (e.g. experiences, beliefs, goals, personality, etc.) are instrumental in the appraisal and coping process.³⁵⁰ That is, these factors drive what we consider stressful and the mechanism with which we deal with them.³⁵⁰ Essentially, stress is a result of the inability to cope.³⁵⁰

As acknowledged by the Cognitive Theory of Psychological Stress and Coping, individual differences impact the appraisal of potential stressors.³⁵⁰ Individual differences with respect to personality traits are believed to at least partially explain differences in the appraisal and coping processes.³⁵⁰ In particular, the trait of neuroticism is characterized by increased vulnerability or proneness to psychological stress.³⁵² Individuals higher in neuroticism have shown to experience stress “more [frequently]...and more [intensely]”.³⁵² Neuroticism also impacts the coping process.^{352,353} More specifically, neuroticism has been linked to the utilization of poorer coping strategies.³⁵³ There is evidence to suggest that neuroticism is at least partially innate and is relatively consistent.^{336,354} In research, it has served as “an indicator of the cumulative level of psychological distress experienced across the lifespan” and has been used interchangeably with psychological or chronic distress.³³⁶

Neuroticism is also associated with post-traumatic stress disorder (PTSD).³⁵⁵ PTSD arises as a result of severe psychological stress and is characterized by “autonomic/physiological, cognitive, and emotional symptoms”.³⁵⁶ Traumatic experiences can result in either temporary or sustained disturbance, the latter of which has been coined PTSD.³⁵⁵ Individuals higher in neuroticism are predisposed to PTSD.³⁵⁵ PTSD may be associated with AD by way of chronic stress.³⁶⁷ As such, the previously described biological mechanisms linking chronic stress to AD (i.e. HPA-dysfunction, hippocampal damage and atrophy, inflammation) are also believed to explain the association between PTSD and AD.³⁶⁷ Both neuroticism and PTSD serve as indicators or “markers of chronic stress”.^{357,366}

5.2 Objective

This study attempts to systematically review and collate the available epidemiological evidence with respect to the association between psychological stress and stress indicators with risk of AD.

5.3 Literature search strategy

The search strategy was developed in consultation with Lindsay Sikora, an information specialist involved in the National Population Health Study of Neurological Conditions. The search strategy was developed in the MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations databases (1948 – July 2012). The strategy consisted of keywords and MEDLINE controlled vocabulary or “medical subject headings” (meSH) associated with four concepts: disease terminology, risk/risk factor terminology, terminology related to psychological stress, and terminology aimed at identifying observational studies. Terms used for the disease concept were: “Alzheimer*”, “Alzheimer’s disease/”, “dementia/”, “presenile dementia*”, “acute confusional senile dementia”, “senile dementia*”, “primary senile degenerative dementia”, and “primary degenerative senile”. The risk/risk factor concept was integrated using a search filter aimed at restricting the search to studies investigating etiological risk factors. Terms included in the search filter were: “risk/”, “etiology”, and “prevention and control”. Using a methodological search filter, the search was further narrowed to yield observational studies. Terms included in the methodological filter were: “epidemiologic studies/”, “case control studies/”, “cohort studies/”, “Cohort analy\$”, “Follow up adj (study or studies)”, “observational adj (study or studies)”, “longitudinal”, “retrospective”, and “cross-sectional studies/”. Finally, stress-related terminology included: “Stress Disorders”, “Traumatic/ or Stress Disorders”, “Post-Traumatic/ or Stress Disorders”, “Traumatic”, “Acute/ or Stress”, “Psychological/ or stress”. Keywords and mesh terms within each concept were combined using the BOOLEAN operator “OR” while the concepts themselves were combined using the BOOLEAN operator “AND”. The search was limited to humans and a language limit was applied to restrict the search to English and French articles. To maximize the comprehensiveness of the search, additional databases including EMBASE, PsycINFO, Ageline, and CINAHL were also searched. In alternate databases, the search strategy retained its structure; however, database-specific medical subject headings and filters were applied to

ensure compatibility. Medline, EMBASE, and CINAHL were searched from their inception until July 2012. The remaining databases were searched from inception until February 2013.

To minimize the potential for publication bias, the grey literature was searched to identify unpublished systematic reviews.⁴³ The grey literature search involved handsearching two disease-specific journals, namely the International Journal of Alzheimer's disease and the American Journal of Alzheimer's disease and Other Dementias, an internet search of Google and GoogleScholar, and handsearching relevant articles. A search of the grey literature was conducted in February 2013. Refer to Appendix C-1 for the grey literature and database specific search strategies.

5.4 Selection Criteria

The retrieved studies were exported from the databases into a reference management software package (Reference Manager, version 10.0; Thomas Reuters; New York, NY). Once imported into Reference Manager 10.0, the retrieved articles were then exported into DistillerSR, an internet-based screening and data extraction tool (DistillerSR, Evidence Partners, Ottawa, Canada).

A two-tiered approach was employed for study screening in DistillerSR. In the primary screening level, the title and abstract of identified studies were examined. Studies deemed relevant or potentially relevant advanced to the secondary screening level. At this stage, the study was examined in its entirety and eligibility was determined based on a priori established selection criteria. Relevancy was established according to selection criteria pertaining to the population, exposure, outcome and study design. With respect to study populations, cohort studies examining adults with "normal cognition" were eligible for inclusion. Studies examining psychological stress, stress subtypes, and indicators of stress were included. To remain consistent with research practices, studies were required to ascertain the outcome, a clinical diagnosis of AD, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR), the Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders (NINCDS-ADRDA), and the World Health Organization's (WHO) International Classification of Diseases (10th revision, ICD-10).^{358,359} Finally, only case-control and cohort studies were eligible for inclusion.

Studies satisfying the following criteria were eligible for inclusion:

- **Population** – Adults. For cohort studies, adults had to be free of cognitive impairment at baseline²⁰

- **Exposure** – Psychological stress, stress subtypes, and stress indicators
- **Outcome**– Diagnosis of Alzheimer’s disease according to neuropathologic examination or widely accepted criteria, namely, the criteria of the Diagnostic and Statistical Manual of Mental Disorders, third (DSM-III) or fourth edition (DSM-IV-TR), the Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders (NINCDS-ADRDA), or the World Health Organization’s (WHO) International Classification of Diseases (10th revision, ICD-10).
- **Study Design** –Case-control and cohort studies.

Studies were excluded from the review if any of the following criteria were satisfied:

- The outcome of interest was cognitive decline, Mild Cognitive Impairment (MCI) or non-AD dementias (ex. Frontotemporal dementia, Pick’s disease, Lewy body dementia, Vascular dementia, Creutzfeldt-Jakob disease)
- The study failed to distinguish AD from all-cause dementia or dementia subtypes (e.g. study reported on risk of all-cause dementia and did not provide risk estimates for Alzheimer’s disease)
- AD was not diagnosed according to NINCDS-ADRDA, ICD, or DSM criteria
- Study did not report risk estimates or did not provide sufficient data to generate a risk estimate
- Study was focused on progression from MCI to AD (i.e. study examines cognitively impaired subjects)
- Although anxiety and psychological stress are “related constructs”, studies that solely reported on the effect of anxiety were excluded.³⁶⁰
- The study employed an alternative methodological design (e.g. cross-sectional studies, ecological studies, narrative reviews, etc.)
- Full article could not be obtained

5.5 Study Selection Method

To minimize the biased inclusion of studies, duplicate screening was employed for both screening levels. The “liberal accelerated” duplicate screening process, employed in the conduct of systematic reviews by the Ottawa Methods Center, was used.⁴⁶ Briefly, only studies that were eliminated by the lead reviewer underwent independent review by a second reviewer. The liberal

accelerated method was employed to reduce the number of articles that required duplicate screening thereby resulting in a more efficient use of resources.⁴⁶ In the event of discordance, the study in question was re-examined by both reviewers and a decision was reached through consensus. Studies that satisfied the selection criteria advanced to the quality assessment phase of the review.

5.6 Quality Appraisal

The methodological quality of identified studies was evaluated according to the Newcastle-Ottawa Scale (NOS) which considers the selection of subjects, methods for exposure and outcome ascertainment, adequacy of confounding adjustment, and the duration and completeness of follow-up (where applicable).³⁶¹ The instrument is a nine-point scale with higher scores denoting superior methodological quality. The scale is divided into two sections for the evaluation of cohort and case-control studies. The scale is further divided into the following domains: selection, comparability, and outcome with the latter domain replaced by “exposure” for the evaluation of case-control studies. Due to its subjectivity, the following clarifications were made a priori.

With respect to cohort studies, a point (or star) was assigned to the first item of the “selection domain” if the exposed subjects were representative of the average stressed subject in the community.³⁶¹ One point was assigned to this first item if the exposed cohort was either “truly” or “somewhat” representative.³⁶¹ Because stress is a universal phenomenon, population-based cohort studies were considered most likely to recruit subjects who were “truly” representative of the average stressed subject in the community. A similar criterion, with respect to assigning a point to population-based studies, was employed in a previous systematic review.³⁶² Studies which recruited subjects from the community, without restricting recruitment to a “specific group”, were considered “somewhat representative”.³⁶¹ A point was assigned to the second item of the tool if non-exposed subjects were derived from the same source as exposed subjects.³⁶¹ Use of medical records or structured interviews for exposure ascertainment justified a point for the third item of the domain. Studies which utilized self-administered questionnaires were not eligible for a point.³⁶¹ A point was assigned to the final item of the “selection” domain if exclusion of prevalent cases at baseline was explicitly stated. With respect to the second domain of the instrument, “comparability”, one point was assigned if the study minimally adjusted for the confounding effect of demographic variables, namely age and sex. A second point was assigned if additional adjustments for vascular (e.g. hypertension, diabetes) and/or lifestyle factors (e.g. physical activity, smoking) were conducted. A point was assigned to the first item of the “outcome” domain if AD was ascertained according to

“independent or blind assessment” or according to medical records using relevant ICD-9 codes.³⁶¹ To remain consistent with previous research, adequate length of follow-up was defined as a minimum of two years (for studies on AD).²⁰ For the final item, follow-up rates exceeding 80% was selected as an acceptable threshold.³⁶³ Studies that reported complete follow-up of all subjects (100%) or rates exceeding 80% were assigned a point.

With respect to case-control studies, a point was assigned to the first item of the selection domain if AD was ascertained according to data obtained from a clinical diagnostic work-up. Evaluation of comparability remained consistent with the criteria used for cohort studies. The remaining items were assessed according to the criteria specified in the instrument.

Individual item scores were summed to obtain a total quality score. Studies were then categorized as high (8-9 points), moderate (6-7), or low (≤ 5 points) according to previously employed thresholds.³⁶⁴ Quality assessment was conducted independently by two reviewers. Refer to Appendix C-2 the Newcastle-Ottawa Scale.

5.7 Data Extraction Strategy

In addition to the study findings (e.g. risk estimates), population (e.g. race/ethnicity, age, sex) and methodological (e.g. study design, length of follow-up, source of participants, exposure/outcome ascertainment) characteristics were extracted. To minimize the potential for bias, data was independently extracted by two reviewers. In the event of discordant data collection, concordance was attained through discussion.

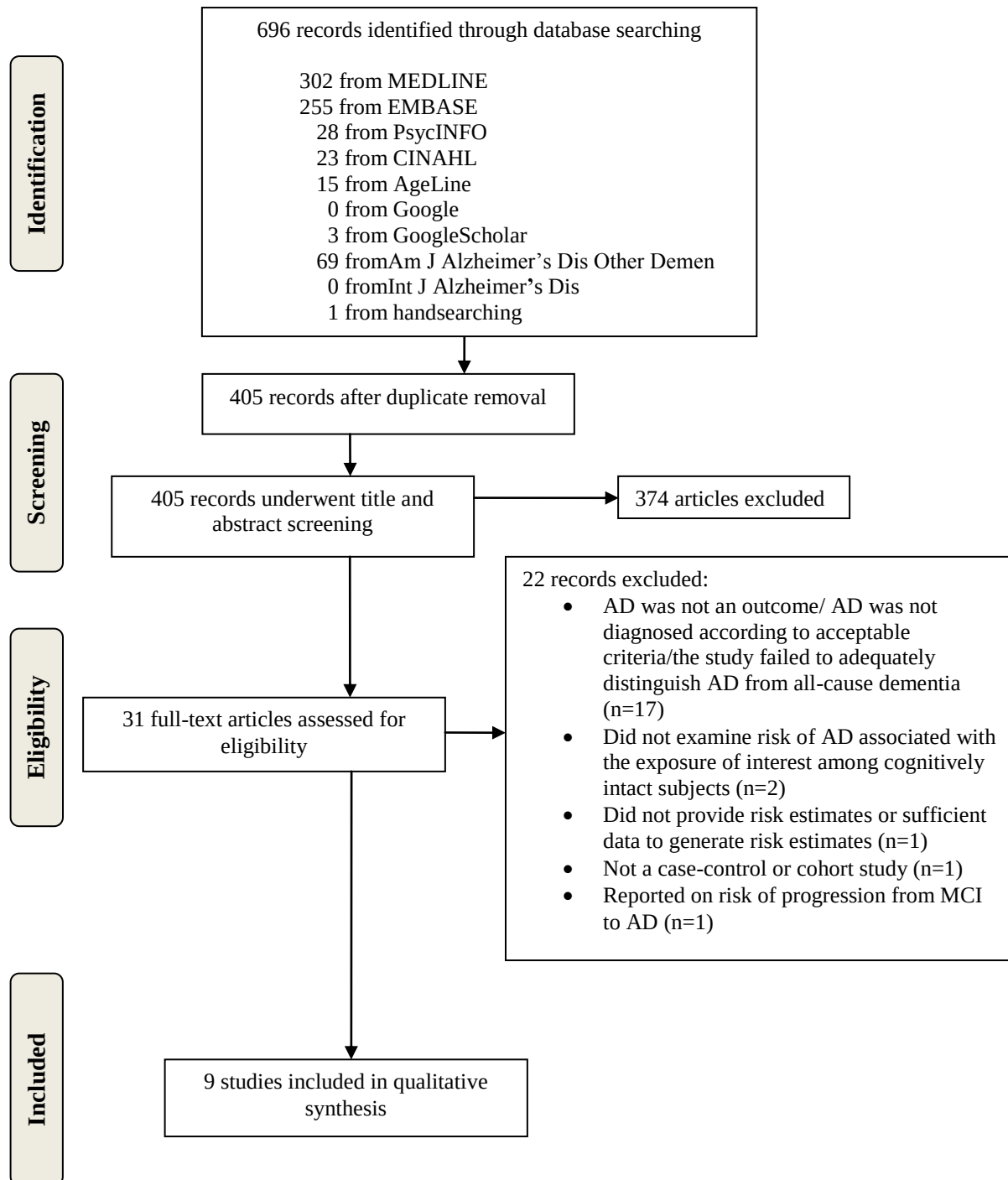
5.8 Literature Search Results

The database search yielded 623 articles. Of these studies, 302 citations were retrieved from MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations databases, 255 from EMBASE and EMBASE Classic, 23 from CINAHL, 28 from PsycINFO, and 15 from AgeLine. An additional 72 records were identified through the grey literature search. One additional study³⁶⁵ was identified through hand searching the reference list of relevant studies. A total of 405 unique records remained following the duplicate citation removal process in DistillerSR. Of the 405 studies, 374 were deemed irrelevant based on a review of the title and abstract and were consequently excluded.

Of the remaining 31 studies eligible for full article screening, nine studies satisfied the inclusion criteria and were included in the qualitative synthesis. Of the remaining 22 studies, 17

were excluded because AD was not an outcome of the study, AD was not diagnosed according to acceptable criteria, or the study failed to adequately distinguish AD from all-cause dementia (i.e. risk estimates for AD were not reported). Two studies were excluded because they did not examine risk of AD associated with the exposure of interest. The remaining three studies were excluded because the study did not utilize the case-control or cohort design, the study examined risk of progression from mild cognitive impairment to AD, or risk estimates were not reported or there was a lack of sufficient data to generate a risk estimate. Refer to Figure 5 for the flow of studies at each stage of the review process. A list of the 22 studies excluded in the secondary screening phase, along with reasons for exclusion, can be found in Appendix C-3. Refer to Appendix C-4 for a list of included studies.

Figure 5 - PRISMA Flow Diagram: De Novo Systematic Review



PRISMA Template Source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement*. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

5.9 Clinical and Methodological Characteristics

Included studies were conducted in Sweden^{343,365,366} or the United States of America^{336,367,368,369,370,371}. Although the ethnic or racial origin of participants was not adequately described in most studies, based on the locations of the included studies, it is apparent that a majority of the participants were Caucasian. Two studies by Wilson et al.^{336,368} specifically indicated the inclusion of African-American participants. Age of participants at baseline ranged from 47.0 to over 90 years of age.

Three^{336,369,370} studies were community-based and four^{343,365,366,368} were population-based studies. The remaining studies by Duberstein and Yaffe et al. examined subjects recruited from the Ginko Evaluation of Memory (GEM) randomized trial³⁷¹ and veterans assessed in U.S. Department of Veterans Affairs medical centers³⁶⁷, respectively. Seven^{336,343,365,368,369,370,371} of the nine studies employed a prospective cohort design and one³⁶⁷ was a retrospective cohort study. The remaining study³⁶⁶ utilized data from a population-based cohort but was analyzed as both a case-control and co-twin (matched pair case-control study comparing “discordant” twins with respect to dementia status³⁶⁶) study. Among the prospective cohort studies, length of follow-up ranged from 2.7 to 35 years. Six cohort studies reported data pertaining to follow-up rates or losses to follow-up. Among three studies reported by Wilson et al.^{336,369,370} follow-up data was available for 98.9%, 92.8%, and 95.7% of all eligible subjects, respectively. Johansson et al.³⁴³ reported participation rates of 91%, 83%, 70% and 71% for the four follow-up assessments of the Prospective Population Study of Women, respectively. Of the 1473 subjects available in the Kungsholmen Project, 325 subjects were unavailable for follow-up assessments due to death, unwillingness, or emigration.³⁶⁵ Finally, Yaffe et al. reported that outcome status could not be ascertained for 13.1% of available subjects as they “were not seen at a VA health care facility during the follow-up period”.³⁶⁷ The characteristics and findings of the identified studies are summarized in Table 22.

Table 22 - Characteristics and findings of the included studies

Source, Study Location, Study design	Study population	Sample size (cases/N)	Mean age at baseline (years) or Age range, % Female	Average length of follow-up (years)	Risk factor Method for stress ascertainment Respondent	Diagnostic criteria	Covariates	Results, Risk estimate (95% CI)
Andel et al. ³⁶⁶ Sweden Cohort study	Elderly persons from the "population-based registry of all twins residing in Sweden"	167/10106	72.7 (SD = 6.2), 52%	N/A	Work-related stress, Telephone interview, Participant or proxy respondent ("a spouse or adult child")	NINCDS-ADRDA	Age (at screening), sex, education, vascular disease, work complexity, manual work	(a) Lower job control (OR: 1.04; 95% CI: 0.88, 1.23) (b) Lower social support (OR: 1.22; 95% CI: 1.02, 1.46) (c) Greater job strain (OR: 0.95; 95% CI: 0.79, 1.13)
Wang et al. ³⁶⁵ Stockholm, Sweden Cohort study	Elderly persons participating in the population-based Kungsholmen Project	197/913	75+ 74.3% (non-demented group) 84.3% (AD group)	6.0 (5.4 median) (4298 person-years)	Work-related stress, Questionnaire administered in-person by a nurse, Proxy respondent (spouse or child)	Similar to NINCDS-ADRDA	Age, sex, education, depressive symptoms, vascular disease, APOE	(a) Job control (high job control as referent): Moderate (HR: 2.10; 95% CI: 1.20, 3.90) Limited (HR: 2.20; 95% CI: 1.20, 4.10) Low (HR: 2.30; 95% CI: 1.20, 4.30) Low-to-moderate (HR: 2.20; 95% CI: 1.20, 3.90)

								High job control (continuous variable) - HR: 0.92; 95% CI: 0.81, 1.04 (b) Job demands (high job demands as referent): Moderate (HR: 1.40; 95% CI: 0.90, 2.10) Limited (HR: 1.40; 95% CI: 0.90, 2.20) Low (HR: 1.30; 95% CI: 0.80, 2.10) Low-to-moderate (HR: 1.40; 95% CI: 0.90, 2.00) High job demand (continuous variable) - HR: 0.98; 95% CI: 0.87, 1.10 (c) Job strain (active job strain as referent): Low (HR: 0.50; 95% CI: 0.10, 4.10) Passive (HR: 1.90; 95% CI: 1.03, 3.60) High (HR: 1.90; 95% CI: 1.00, 3.40) Low-to-moderate (HR: 1.40; 95% CI: 0.90, 2.00)

Johansson et al. ³⁴³ Gothenburg, Sweden Cohort study	Female members from the population-based Prospective Population Study of Women	105 /1415	47.0 (SD = 6.0), 100%	35.0 (40 089 person-years)	Midlife psychological stress, Self-reported responses to a single question administered in-person by a physician, Participant	NINCDS-ADRDA	Age, education, marital status, socioeconomic status, having children, smoking, wine consumption, physical activity, coronary heart disease, hypertension and waist-to-hip ratio	(a) Frequent/constant stress vs. No stress reported in 1968 (HR: 2.14; 95% CI: 1.36, 3.38) (b) Frequent/constant stress vs. No stress reported in 1974 (HR: 1.74; 95% CI: 1.09, 2.78) (c) Frequent/constant stress vs. No stress reported in 1980 (HR: 1.58; 95% CI: 0.90, 2.77)
Wilson et al. ³³⁶ USA Cohort study	Elderly members of the Catholic clergy enrolled in the community-based Religious Orders Study	140/797	75.2 (SD = 7.0), 68.4%	4.9	Proneness to psychological distress, 12-item Neuroticism Scale from the NEO Five-Factor Inventory, Participant	NINCDS-ADRDA	Age, sex, education, depressive symptoms	Each one-point increase on the distress proneness scale (HR: 1.05; 95% CI: 1.01, 1.08) Results unchanged when adjusted for depressive symptoms
Wilson et al. ³⁶⁸ Chicago, USA Cohort study	Population-based study of elderly persons residing in Chicago	170 /1064	73.8 (SD= 9.6), 61.9%	3 to 6 ^a	Proneness to psychological distress, 4-item Neuroticism Scale from the NEO Five-Factor Inventory, Participant	NINCDS-ADRDA	Age, sex, race, education, possession of an APOE-e4 allele, and follow-up time, depressive symptoms	Each one-point increase on the distress proneness scale (OR: 1.06; 95% CI: 1.01, 1.11) Results unchanged when adjusted for depressive symptoms

Wilson et al. ³⁶⁹ Chicago, USA Cohort study	Elderly persons from the community-based Rush Memory and Aging Project	55 /648	80.6 (SD= 6.9), 73.5%	2.7	Proneness to psychological distress, 6-item Neuroticism Scale from the NEO Five-Factor Inventory, Participant	NINCDS-ADRDA	Age, sex, education, depressive symptoms	Each one-point increase on the distress proneness scale (OR: 1.06; 95% CI: 1.02, 1.10) Results unchanged when adjusted for depressive symptoms
Wilson et al. ³⁷⁰ Chicago, USA Cohort study	Elderly persons from the community-based Rush Memory and Aging Project	94/785	80.7 (SD = 7.4), 76.3%	3.4 (SD =1.4)	Multiple domains of neuroticism (anxiety, angry hostility, depression, self-consciousness, impulsiveness, vulnerability to stress), 48-item Neuroticism scale from the NEO Personality Inventory-Revised, Participant	NINCDS-ADRDA	Age, sex, education	(a) Anxiety (HR: 1.05; 95% CI: 1.01, 1.09) (b) Angry hostility (HR: 1.00; 95% CI: 0.96, 1.05) (c) Depression: (HR: 1.04; 95% CI: 0.99, 1.08) (d) Self-consciousness (HR: 1.03; 95% CI: 0.98, 1.08) (e) Impulsiveness: (HR: 1.01; 95% CI: 0.96, 1.06) (f) Vulnerability to stress (HR: 1.06; 95% CI: 1.01, 1.12)
Duberstein et al. ³⁷¹ USA Cohort study	Participants enrolled in the Ginkgo Evaluation of Memory (GEM) trial	116/767	78.6 (SD = 3.1), 41.9%	6.1 (median) (4410.6 person-years)	Neuroticism, 12-item Neuroticism Scale from the NEO Five-Factor	NINCDS-ADRDA	Age, gender, race, education, Modified Mini-Mental State Exam score, Center	Each SD increase in neuroticism (HR: 1.36; 95% CI: 1.08, 1.71)

					Inventory, Participant		for Epidemiologic Studies Depression Scale (CES-D) score, hypertension, diabetes, osteoporosis, cancer within past five years, cardio- vascular disease (coronary heart disease, angina, stroke, transient ischemic attack, bypass surgery, angioplasty)	
Yaffe et al. ³⁶⁷ USA Cohort study	Veterans receiving medical care at VA health care facilities	3882/181093	68.8 (SD = 8.6) 3.5%	7.2 (range, 0.1-7.4)	Posttraumatic stress disorder (PTSD), Patient records using ICD-9- CM code of 309.81 (PTSD)	ICD-9-CM code 331.0	Age, sex, race/ethnicity, education, income, hypertension, diabetes, myocardial infarction, cerebro- vascular disease, clinical depression, substance abuse, head injury	HR: 1.71; 95% CI: 1.58, 1.85

^aAverage years of follow-up not provided.

5.10 Exposure ascertainment

Work-related stress was the exposure of interest in two^{365,366} of the included studies while post-traumatic stress³⁶⁷, midlife psychological stress³⁴³, global measures of neuroticism/proneness to psychological stress^{336,368,369,371}, and multiple domains of neuroticism³⁷⁰, including vulnerability to stress, were examined in the remaining seven studies. Although interrelated, differences across these exposure variables warranted differentiation in the qualitative synthesis.

Among the seven prospective studies, the exposure was ascertained according to self-^{336,343,368,369,370,371} or proxy³⁶⁵-reported responses to a questionnaire^{336,365,368,369,370} or a single question³⁴³ administered in-person. In three prospective studies^{343,365,369} the question or questionnaire was administered by a trained professional, namely, a nurse³⁶⁵ or a physician³⁴³. In the retrospective cohort study by Yaffe et al., post-traumatic stress was ascertained according to medical records obtained from the VA National Patient Care Database.³⁶⁷ More specifically, a positive diagnosis of PTSD required an ICD-9 code of 309.81 on a minimum of two visits.³⁶⁷ Finally, work-related stress was ascertained according to a telephone interview completed by the participant or a proxy informant in the Swedish Twins study.³⁶⁶

Among the prospective cohort studies, exposure status was ascertained only at baseline in three^{336,368,369} studies, at baseline and follow-up assessments in one³⁴³ study, and only at the first follow-up assessment in one³⁶⁵ study. The exposure was ascertained at baseline in the study reported by Duberstein et al.³⁷¹; however, it is unclear whether the exposure was re-examined at each follow-up. Timing of exposure ascertainment was unclear in the remaining prospective cohort study³⁷⁰. In the retrospective cohort study by Yaffe et al., PTSD was ascertained during the baseline period.³⁶⁷ Finally, occupational data used to ascertain work-related stress was collected at baseline in the Swedish Twin Registry study³⁶⁶.

5.11 Outcome ascertainment

All cohort studies explicitly stated that dementia and/or AD was ascertained at baseline to exclude prevalent cases. Participants of the Swedish Twin Registry³⁶⁶ were not disease-free at baseline; consequently, prevalent cases of dementia were included in the analysis.

A positive diagnosis of AD was ascertained according to existing medical records in one³⁶⁷ study. In the remaining eight studies, AD was ascertained according to a diagnostic work-up involving psychiatric examination³⁴³, medical history^{336,343,368,369,370}, neurologic/neuropsychological examination^{336,368,369,370,371}, cognitive function testing^{336,368,369}, close informant interviews³⁴³, brain

imaging^{336,368,371}, and other unspecified in-person clinical examinations³⁶⁶. A positive diagnosis of AD was then ascertained according to the NINCDS-ADRDA or similar criteria administered by an experienced neurologist³³⁶, geriatrician³³⁶, geriatric psychiatrist³⁴³, clinician(s)^{365,369,370,371}, or unspecified personnel^{366,368}. Two studies^{343,365} relied on clinical records, death certificates, and hospital discharge records for deceased participants or those lost to follow-up.

5.12 Covariates

All included studies adjusted for the potentially confounding effects of age, sex and educational attainment. Five^{343,365,366,367,371} studies adjusted for vascular risk factors and two^{365,368} considered the effect of APOE genotype.

5.13 Quality Appraisal

All studies were deemed to be of high^{343,365,367,369} or moderate methodological quality according to the NOS. A point was assigned to all but one³³⁶ cohort study for the first item of the instrument which considers the representativeness of the exposed cohort. More specifically, a point was assigned to two^{365,368} studies which examined population-based cohorts, Yaffe et al. earned a point as veterans were considered representative of subjects afflicted with PTSD in the community, and three^{369,370,371} studies were assigned a point for being “somewhat” representative (i.e. subjects recruited from the community). Although the study reported by Johansson et al. was a population-based study, it was restricted to females and was consequently considered only “somewhat representative”. The remaining study³³⁶ was not assigned a point as recruitment was restricted to a “specific group”, namely, members of the Catholic clergy. All cohort studies were assigned a point for the second item of the “selection” domain as non-exposed subjects were consistently recruited from the same source as exposed subjects (i.e. exposed subjects were compared to an internal comparison group³⁷² derived from the same cohort). Three^{343,365,369} studies were assigned a point for ascertaining the exposure according to structured interviews and one³⁶⁷ was allocated a point for relying on medical records. The remaining studies relied on self-administered questionnaires or did not clearly state that the questions were administered by an interviewer. All eight cohort studies were assigned a point for explicitly stating that prevalent cases were excluded at baseline or the cohort was dementia-free at study onset. All studies were allocated a point for controlling for the confounding effect of demographic variables while four^{343,365,367,371} studies were assigned an additional point for adjusting for vascular and/or lifestyle factors. Seven studies were assigned a

point for employing independent or blind³⁷¹ outcome assessment. The remaining study³⁶⁷ was assigned a point for relying on medical records using ICD-9 codes to identify cases. Length of follow-up exceeded two years in all studies. Therefore, all studies were awarded a point for employing an adequate length of follow-up. Three^{336,369,370} studies were assigned a point for reporting follow-up rates exceeding 80%. A point was also assigned to the only retrospective cohort study³⁶⁷ as follow-up data was missing for only 13.1% of subjects. Johansson et al.³⁴³ reported follow-up rates below 80% for two of the four follow-up assessments. Wang et al.³⁶⁵ specified that 325 out of 1238 subjects (those who were not lifetime housewives and who had information on occupation) were deceased (n=153) or lost to follow-up due to refusal or emigration (n=172). Both studies^{343,365} relied on existing records (e.g. medical records, death certificates) to ascertain the outcome for subjects who died³⁶⁵ during the course of the study and/or were otherwise lost to follow-up³⁴³. As Wang et al. was able to ascertain the outcome for subjects who died (n=153), the follow-up rate exceeded 80%. Despite attempts made by Johansson et al.³⁴³ to mitigate losses, the extent to which this improved follow-up rates was unclear. As such, a point was not provided as follow-up rates were below 80% for the last two follow-up assessments. Finally, the remaining studies^{368,371} were not assigned a point as follow-up rates or methods to ascertain the outcome in those lost to follow-up were not specified.

With respect to the study reported by Andel et al., which was analyzed as a case-control study, a point was assigned for relying on a clinical diagnostic workup for outcome ascertainment, a point was assigned to the second item as all eligible cases (i.e. those deemed cognitively impaired by a screening test) were assessed for dementia, a point was assigned to the third item as controls were derived from the same population as cases (Swedish Twin Registry), a point was assigned to the fourth item as controls were free of dementia, and two points were assigned for comparability as demographic variables and vascular risk factors were controlled for in analyses. A point was not assigned to the remaining items as the exposure was ascertained according to telephone interview without specifying that the interviewer was blind to outcome status, different methods were employed for exposure ascertainment of cases and controls, and non-response rates were not specified, although characteristics of non-participants were described.³⁶⁶ Refer to Table 23 and Table 24 for a tabular summary of the quality appraisal of relevant studies.

Table 23 - Quality appraisal of cohort studies according to Newcastle-Ottawa Scale[§]

Source	Selection				Comparability	Outcome			Total Score
	Representativeness of Exposed Cohort	Selection of the Nonexposed Cohort	Ascertainment of Exposure	Exclusion of Prevalent Cases	Comparability of Cohorts	Assessment of Outcome	Adequate Length of Follow-up	Completeness of Follow-up	
Wang et al.	A(*)	A(*)	B(*)	A(*)	A and B(**)	A(*)	A(*)	B(*)	9
Wilson et al., 2003	C	A(*)	C	A(*)	A(*)	A(*)	A(*)	B(*)	6
Wilson et al., 2005	A(*)	A(*)	C	A(*)	A(*)	A(*)	A(*)	D	6
Wilson et al., 2006	B(*)	A(*)	B(*)	A(*)	A(*)	A(*)	A(*)	B(*)	8
Wilson et al., 2011	B(*)	A(*)	C	A(*)	A(*)	A(*)	A(*)	B(*)	7
Duberstein et al.	B(*)	A(*)	C	A(*)	A and B (**)	A(*)	A(*)	D	7
Johansson et al.	B(*)	A(*)	B(*)	A(*)	A and B(**)	A(*)	A(*)	C	8
Yaffe et al.	A(*)	A(*)	A(*)	A(*)	A and B(**)	B(*)	A(*)	B(*)	9

[§]Letters denote the selected option for each item of the NOS (see instrument). Stars (*) denote a point.

Table 24 - Quality appraisal of case-control studies according to Newcastle-Ottawa Scale[§]

Source	Selection				Comparability	Exposure			Total Score
	Adequacy of case definition	Representativeness of cases	Selection of controls	Definition of controls	Comparability	Ascertainment of exposure	Same methods for exposure ascertainment of groups	Non-response rate	
Andel et al.	A(*)	A(*)	A(*)	A(*)	A and B(**)	C	B	B	6

5.14 Statistical Analyses

Studies varied with respect to the measure or type of stress under examination. This source of methodological heterogeneity precluded a meta-analysis. Alternatively, studies were summarized qualitatively.

5.15 Study Findings

5.15.1 Proneness to Psychological Stress, Neuroticism

Four longitudinal cohort studies^{336,368,369,370} reported by the same author examined the association between proneness or vulnerability to psychological distress, ascertained in late-life, and the risk of AD. In the earliest study³³⁶, participants were recruited from the Religious Orders Study, a community-based cohort study of elderly members of the Catholic clergy. The 2005 population-based study examined a racially diverse sample recruited “from a geographically defined area of Chicago”³⁶⁸, while the 2006 and 2011 studies recruited participants from the community-based Rush Memory and Aging Project^{369,370}. Neuroticism served as an indicator of proneness to psychological stress in all four studies. The exposure was ascertained according to self-reported responses on the Neuroticism Scale from the NEO Five-Factor Inventory. However, variations of the instrument were employed across the four studies. More specifically, a 12-item version of the instrument was employed in the 2003 study³³⁶, a 4-item version in the 2005 study³⁶⁸, a 6-item version in the 2006 study³⁶⁹, and a 48-item version in the most recent study³⁷⁰. Respondents were required to assign a score ranging from 0 to 4 on each item of the instrument and scores from each item were summed to obtain a total score of proneness/vulnerability to psychological distress³³⁶. Three studies^{336,368,369} considered the effect of proneness to psychological stress using a global score of neuroticism while the remaining study³⁷⁰ examined the effect of each domain of neuroticism, including vulnerability to stress. The 12-item version has shown to have “good reliability and convergent validity in a variety of samples”.³⁷³ Both the 4- and 6-item scales are considered to have good validity as they correlate well with the 12-item scale (4-item: $r = 0.86$; 6-item: $r = 0.90$; $p < 0.001$).^{368,369} The 48-item scale from the NEO PI-R has shown to have “good internal consistency and test-retest stability”.³⁷⁴ A clinical diagnosis of AD was ascertained according to the NINCDS-ADRDA following clinical and neurologic examination. Finally, three^{336,369,370} of the four studies examined the association between distress proneness and AD pathology using autopsy results from participants who died during the course of the study.

According to the results of the 2003 study, a total of 140 of the 797 participants recruited from the Religious Orders Study developed AD (mean follow-up = 4.9 years).³³⁶ Multivariable-adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs. In the model adjusted for age, sex, and education, there was a 6% increased risk of AD associated with “each 1-point increase in distress proneness” (HR: 1.06; 95% CI: 1.02, 1.09).³³⁶ Considered categorically, proneness to psychological stress (score of 24 vs. score of 11) increased risk of AD by 2.00 times (95% CI: not provided).³³⁶ To examine the association between psychological stress and AD pathology, histopathological hallmarks of AD were ascertained according to neuropathological examination.³³⁶ The number of neuritic plaques, diffuse plaques, and neurofibrillary tangles from four areas of the brain was determined and a global score was derived.³³⁶ The association was determined using a linear regression model. Although distress proneness was significantly associated with clinical AD, the study failed to detect an association between distress proneness and AD pathology (estimate = -0.214, SE = 0.814, $p = 0.793$).³³⁶

Distress proneness was also associated with an increased risk of AD in the 2005 study.³⁶⁸ In the community-based sample of 1064 participants, a total of 170 subjects were diagnosed with AD over the 3 to 6 years of follow-up.³⁶⁸ The association between distress proneness and AD was estimated according to logistic regression analysis. Each one point increase in distress proneness was associated with an increased odds of AD (OR: 1.06; 95% CI: 1.01, 1.11).³⁶⁸ Considered categorically, there was a 2.40 times increased risk of AD associated with high (vs. low) distress proneness.³⁶⁸ According to stratified analysis, each one unit increase in distress proneness was associated with a statistically significant 12% increased odds of AD in Caucasians (OR: 1.12; 95% CI: 1.05, 1.19). The association failed to reach statistical significance for African Americans (OR: 1.02; 95% CI: 0.97, 1.08).³⁶⁸

Using a sample of subjects from the Rush Memory and Aging Project, the 2006 study by Wilson et al.³⁶⁹ replicated earlier findings. During a mean follow-up of 2.7 years, 55 of 648 subjects developed AD. Multivariable-adjusted Cox proportional hazards models were used to estimate the association between distress proneness and AD. Each unit increase in distress proneness was associated with a 6% (RR: 1.06; 95% CI: 1.02, 1.10) increased risk of AD.³⁶⁹ Considered categorically, there was a 2.70 times increased risk of AD associated with high (score = 24) distress proneness.³⁶⁹ The association between distress proneness and AD pathology was determined using a linear regression model. The autopsy analysis replicated previous findings suggesting that distress proneness was not associated with histopathological indicators of AD (estimate = 0.010, SE = 0.013, $p = 0.440$).³⁶⁹

Using a sample of subjects from the Rush Memory and Aging Project, the most recent study by Wilson et al. examined the risk of AD associated with six domains of neuroticism, namely, depression,

angry hostility, self-consciousness, impulsiveness, anxiety, and vulnerability to stress.³⁷⁰ Of 785 participants, 94 developed AD (mean follow-up = 3.4 years; SD = 1.4). Multivariable-adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs. According to the results of the study, angry hostility, depression, self-consciousness, and impulsiveness were not significantly associated with risk of AD.³⁷⁰ Each unit increase in anxiety score, however, was associated with a marginally significant 5% increased risk of AD (HR: 1.05; 95% CI: 1.01, 1.09).³⁷⁰ Of particular importance, there was a marginally significant 6% increased risk of AD associated with each unit increase on the vulnerability to stress scale (HR: 1.06; 95% CI: 1.01, 1.12).³⁷⁰ Treated categorically, high vulnerability to stress (score = 15 vs. score = 5) was associated with a 79% increased risk of developing AD.³⁷⁰ Finally, the association between each domain of neuroticism and the histopathological indicators of AD were examined according to linear regression analysis using brain autopsy data obtained from 156 deceased subjects.³⁷⁰ There was no association between AD pathology and indicators of neuroticism.³⁷⁰

It is important to note that the confidence intervals reported in the Wilson et al. studies^{336,368,369,370} are likely incorrect. The confidence intervals reported are narrow relative to the number of reported AD cases. Other included studies (e.g. by Yaffe et al.³⁶⁷) with significantly higher number of events reported wider confidence intervals.

The prospective cohort study by Duberstein et al. examined the association between personality domains, namely neuroticism, extraversion, openness to experience, conscientiousness, and agreeableness, and risk of developing AD.³⁷¹ The exposure was ascertained according to self-reported responses on the 12 item NEO Five-Factor Inventory. As discussed previously, this 12-item scale has good psychometric properties.³⁷³ As an indicator of chronic stress, neuroticism is the personality domain of interest in the present review. Multivariable-adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs. Of the 767 participants recruited from the Ginkgo Evaluation of Memory (GEM) study, 116 developed AD over the course of follow-up (median = 6.1 years).³⁷¹ Results of the multivariate analysis suggested that each standard deviation increase in neuroticism score was associated with a 36% increased risk of AD (HR: 1.36; 95% CI: 1.08, 1.71).³⁷¹

5.15.2 Mid-life Psychological Stress

The study by Johansson et al. examined the association between midlife psychological stress and risk of AD.³⁴³ Subjects were participants of the Prospective Population Study of Women. Baseline assessments were conducted in 1968/9 and follow-up was conducted in 1974/5, 1980/1, 1992/3, and

2000/3 for a total of 35 years of follow-up.³⁴³ A total of 105 participants were diagnosed with incident AD over the course of the study. Multivariable-adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs. In the fully adjusted analysis, the index group (i.e. those reporting frequent or constant stress at baseline) had a 2.14 times (95% CI: 1.36, 3.38) increased risk of AD when compared to those reporting no stress.³⁴³ Those reporting frequent or constant stress during the first follow-up (1974) had a 1.74 times (95% CI: 1.09, 2.78) increased risk of AD in comparison to those reporting no stress.³⁴³ However, frequent or constant stress reported in 1980 was not significantly associated with risk of AD (HR: 1.58; 95% CI: 0.90, 2.77).

In additional analyses, AD cases were stratified according to cardiovascular disease status. AD cases were classified as either 'AD cases with cerebrovascular disease' (n=73) or 'AD cases without cerebrovascular disease' (n=32). Frequent or constant stress reported in 1968 was associated with an increased risk of AD without cerebrovascular disease (HR: 2.03; 95% CI: 1.16, 3.54).³⁴³ However, those who reported experiencing frequent or constant stress during follow-up in 1974 and 1980 were not at a significantly increased risk of developing AD without cerebrovascular disease (1974 - HR: 1.54; 95% CI: 0.87, 2.67. 1980 - HR: 1.30; 95% CI: 0.64, 2.64). Frequent or constant stress reported at baseline (HR: 2.79; 95% CI: 1.25, 6.25) and at follow-up in 1974 (HR: 2.70; 95% CI: 1.13, 6.45) was associated with an increased risk of Alzheimer's disease with cerebrovascular disease. However, the risk estimate for the 1980 follow-up failed to reach statistical significance (HR: 2.35; 95% CI: 0.88, 6.27). Finally, self-reported stress at multiple follow-up assessments was associated with a 2.33 times (95% CI: 1.41, 3.85) increased risk of AD, a two-fold (HR: 2.02; 95% CI: 1.07, 3.80) increased risk of AD without cerebrovascular disease, and a greater than three-fold increased risk of AD with cerebrovascular disease (HR: 3.28; 95% CI: 1.40, 7.71).³⁴³

5.15.3 Post-traumatic Stress Disorder (PTSD)

The retrospective cohort study by Yaffe et al. examined the association between posttraumatic stress disorder and risk of dementia and dementia subtypes among older veterans who utilized medical services offered by the Department of Veterans Affairs.³⁶⁷ Among the 181093 eligible veterans, 53155 subjects had PTSD and 3882 were diagnosed with AD. Follow-up duration was 7.2 years (range, 0.1-7.4). Multivariable-adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs. According to the fully adjusted model, PTSD was associated with a statistically significant 71% increased risk of AD (HR: 1.71; 95% CI: 1.58, 1.85).³⁶⁷

5.15.4 Work-related Stress

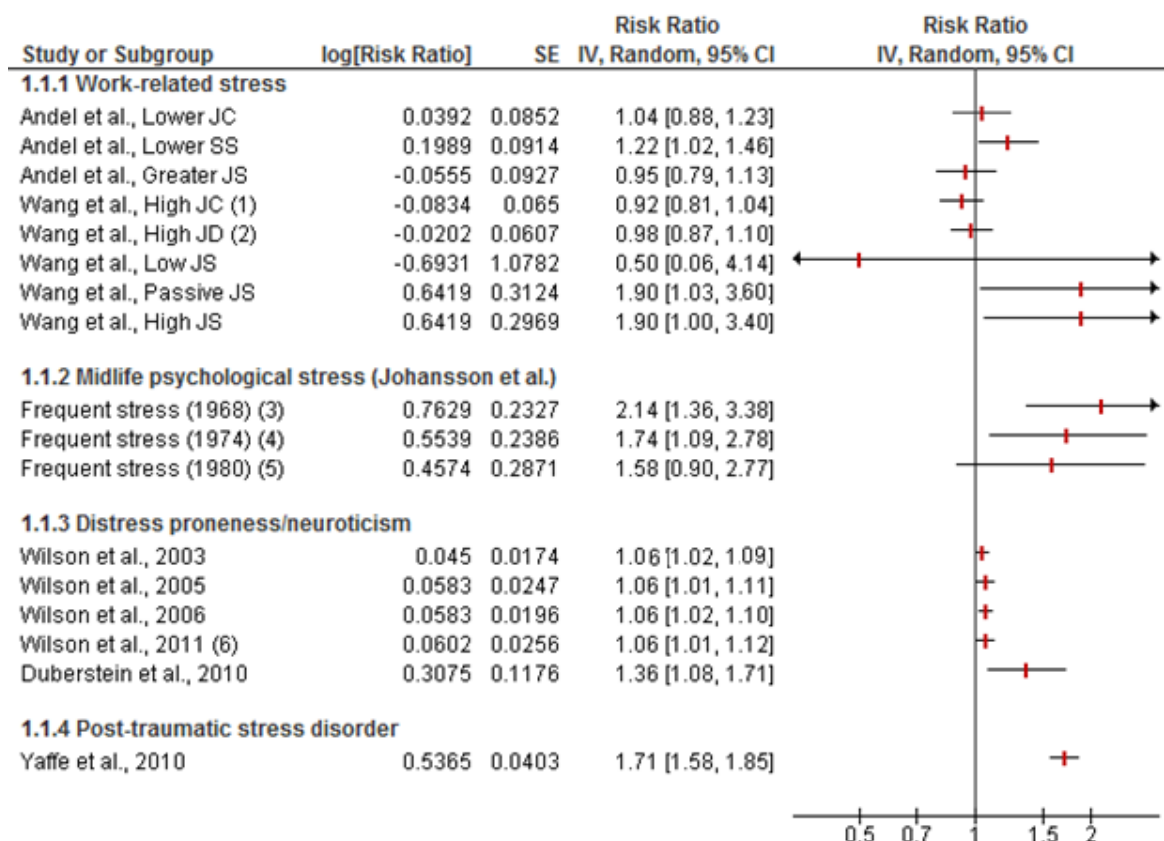
Two population-based studies^{365,366} examined the association between work-related stress and risk of AD. Work-related stress was defined according to the job strain model in both studies.^{365,366} The model uses low job control, low job demand, and low social support as indices of work-related stress.³⁶⁶ Employing this model, the association between AD and the indices, namely, job control, job strain, job demands and/or social support were examined. Data pertaining to occupational history was obtained via telephone interview completed by the participant or by a proxy respondent ("a spouse or an adult child") for cognitively impaired subjects in one study³⁶⁶ and according to proxy respondent responses for all subjects in the second study³⁶⁵. Work-related stress was then ascertained using a validated psychosocial job exposure matrix.^{365,366}

The Swedish Twin study examined the association between work-related stress and prevalent dementia/AD. According to the matched pair case-control analysis of the Swedish Twins study, discordant twins did not differ with respect to all indicators of work-related stress (*Job control*: Mean difference = -0.02, *t*(53): 0.11, *P* = 0.91. *Job demands*: Mean difference = 0.01, *t*(53): 0.05, *P* = 0.96. *Social support*: Mean difference = 0.15, *t*(53): 0.80, *P* = 0.43. *Job strain*: Mean difference = -0.02, *t*(53): 0.37, *P* = 0.71).³⁶⁶ Findings from the matched pair case-control analysis pertain to all-cause dementia and are not specific to AD. Results of the overall case-control analysis (cases: *n* = 257; controls: *n* = 9849) suggest that lower job control (OR: 1.04; 95% CI: 0.88, 1.23) and greater job strain (OR: 0.95; 95% CI: 0.79, 1.13) were not associated with risk of AD.³⁶⁶ Lower social support, however, was associated with a 22% increased risk of AD (OR: 1.22; 95% CI: 1.02, 1.46). In stratified analysis by sex, lower job control and greater job strain were not associated with risk of dementia among males (*Lower job control* - OR: 0.96; 95% CI: 0.72, 1.27. *Greater job strain* - OR: 1.03; 95% CI: 0.71, 1.48) or females (*Lower job control* - OR: 1.14; 95% CI: 0.93, 1.40. *Greater job strain* - OR: 0.97; 95% CI: 0.81, 1.16).³⁶⁶ Although lower social support was associated with an approximately 26% increased risk of AD in females, the association failed to reach statistical significance in males (*Females* - OR: 1.26; 95% CI: 1.01, 1.57. *Males* - 1.25; 95% CI: 0.95, 1.64). In the analysis stratified by work complexity, all three indicators of work-related stress were not associated with risk of AD in occupations with low (*Lower job control* - OR: 1.15; 95% CI: 0.91, 1.45. *Lower social support* - OR: 1.21; 95% CI: 0.98, 1.48. *Greater job strain* - OR: 0.97; 95% CI: 0.78, 1.19) and high (*Lower job control* - OR: 0.98; 95% CI: 0.78, 1.24. *Lower social support* - OR: 1.18; 95% CI: 0.98, 1.42. *Greater job strain* - OR: 1.06; 95% CI: 0.82, 1.37) work complexity.³⁶⁶ In the analysis stratified by type of work, lower job control and greater job strain were not associated with AD among those involved in manual (*Lower job control* - OR: 1.06; 95% CI: 0.87, 1.27.

Greater job strain - OR: 0.94; 95% CI: 0.77, 1.15) and non-manual (*Lower job control* - OR: 1.26; 95% CI: 0.74, 2.15. *Greater job strain*- OR: 1.13; 95% CI: 0.80, 1.60) work.³⁶⁶ Lower social support, however, was associated with an increased risk of AD among manual workers (OR: 1.29; 95% CI: 1.09, 1.53) but not among nonmanual workers (OR: 0.69; 95% CI: 0.34, 1.42). Considered cumulatively, the Swedish Twins study found that lower social support at work was the only indicator of work-related stress that was significantly associated with an increased risk of AD.³⁶⁶ Stratified analysis concluded that lower social support was associated with AD in females and manual workers only.³⁶⁶ Despite findings from previous studies which suggest a protective effect of highly complex occupations against the development of dementia, Andel et al. failed to detect a significant association between indicators of work-related stress and AD irrespective of work complexity.³⁶⁶

According to the Kungsholmen study³⁶⁵, when high job control was used as a referent, lower quartiles of job control were associated with increased risk of AD in the analysis adjusted for age, gender, and education (*Moderate* – HR: 2.10; 95% CI: 1.20, 3.90. *Limited* – HR: 2.20; 95% CI: 1.20, 4.10. *Low*– HR: 2.30; 95% CI: 1.20, 4.30). When the three lower quartiles were collapsed, low-to-moderate job control was associated with a greater than two-fold increased risk of AD when compared to high job control (HR: 2.20; 95% CI: 1.20, 3.90).³⁶⁵ However, high job control was not significantly protective against AD when treated as a continuous variable (HR: 0.92; 95% CI: 0.81, 1.04).³⁶⁵ Lower quartiles of job demands were not associated with risk of AD. There was no association between high job demand and risk of AD when the variable was considered continuously (HR: 0.98; 95% CI: 0.87, 1.10). With respect to job strain, only passive job strain, defined as a product of low job demand and low job control, was associated with a statistically significant increased risk of AD according to the multivariate analysis adjusting for age, gender, education, depressive symptoms and vascular factors (HR: 1.90; 95% CI: 1.03, 3.60).³⁶⁵ High job strain, a product of high job demand and low job control, was marginally associated with AD risk (HR: 1.90; 95% CI: 1.00, 3.40) when compared to the reference category of active job strain (high job demands and high job control). There was no evidence of effect modification by APOE status.³⁶⁵ These findings are summarized in Table 22 and Figure 6.

Figure 6 - Forest plot of available studies on psychological stress and AD



- (1) Treated as continuous variable
- (2) Treated as continuous variable
- (3) Reported in 1968
- (4) Reported in 1974
- (5) Reported in 1980
- (6) Vulnerability to stress domain

5.16 Discussion

The systematic review provides limited evidence regarding the association between stress (i.e. psychological, work-related), stress indicators (i.e. PTSD, neuroticism), and risk of AD. Using an all-female sample, Johansson et al. reported an increased risk of AD associated with frequent or constant psychological stress during midlife while findings from Yaffe et al., which examined an almost entirely male sample of veterans, detected a 71% increased risk of AD associated with post-traumatic stress.^{343,367} Both studies reporting on occupational stress detected an association between AD and at least one marker of work-related stress. Results from the Swedish Twins study suggest that lower support at work but not lower job control or greater job strain were associated with increased risk of AD.³⁶⁶ The Kungsholmen project detected an increased risk of AD associated with lower quartiles of job control and with both passive and high job strain.³⁶⁵ Using three cohorts, Wilson et al. consistently demonstrated that both global measures and specific domains of neuroticism, “an indicator of the cumulative level of psychological distress experienced across the lifespan”, was associated with a marginally significant increased risk of incident AD.^{336,368,369} The most recent study by Wilson et al. found that only two domains of neuroticism, namely anxiety and vulnerability to stress, were significantly associated with AD.³⁷⁰ Furthermore, results reported by Duberstein et al., suggesting an increased risk of AD associated with increasing neuroticism, were consistent with results reported in the four publications by Wilson et al.³⁷¹

An important strength of the present review is attributed to the prospective cohort design of a majority of the included studies. Although these studies are less susceptible to sources of bias inherent in retrospective cohort or case-control studies, such as recall and prevalence-incidence bias, they are susceptible to alternative sources of bias which may compromise their internal validity.³⁷⁵ In particular, cohort studies may be susceptible to selection bias arising from losses to follow-up.³⁷⁵ Because complete follow-up is difficult to achieve, follow-up rates exceeding 80% is routinely recommended to mitigate the potential for selection bias.²⁴⁵ All three studies by Wilson et al. reported rates close to or greater than the recommended follow-up rate.²⁴⁵ However, Johansson et al. reported follow-up rates below the 80% threshold for two of the four follow-up assessments. If losses to follow-up in any of the included studies were differential, the studies may be susceptible to selection bias. Two studies^{343,365} attempted to maximize the completeness of follow-up and ultimately mitigate the potential for selection bias by relying on clinical records, death certificates, and hospital discharge records for deceased participants or those lost to follow-up. However, such attempts may not entirely eliminate the potential for selection bias.

Selection bias may also arise in case-control studies. The Swedish Twin study³⁶⁶ analyzed prevalent dementia cases. As such, the study is susceptible to prevalence-incidence (Neyman) bias, a form of selection bias that arises due to the inclusion of prevalent cases in etiologic research studies.^{366,376} The analysis of prevalent cases may bias the true association between work-related stress and AD and give rise to a spurious risk estimate. Reliance on prevalent cases increases the likelihood of recall error and makes it difficult to distinguish whether the exposure is associated with incidence or survival.^{376,377,378} If the exposure is associated with survival or delayed progression, the exposure would be “overrepresented” in prevalent cases.³⁷⁶ Consequently, the measure of association would be biased away from the null resulting in higher risk estimates.³⁷⁹ Alternatively, if work-related stress is associated with hastened progression of AD and subsequent death, there would be an “underrepresentation” of exposed cases in the study resulting in an observed association that is biased towards the null.^{376,379}

Results of the included studies may also be susceptible to outcome misclassification error attributed to the complexity of outcome ascertainment in dementia research.²¹ Because AD can only be definitively diagnosed post-mortem according to neuropathological examination, antemortem diagnoses of probable or possible AD can only be achieved according to clinical criteria.²¹ A clinical diagnosis of AD is most commonly achieved using the criteria established by the Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders (NINCDS-ADRDA).²¹ Data obtained from several sources, namely, “medical history; neurologic, psychiatric, and clinical examinations; neuropsychological tests; and laboratory studies” are used to guide the diagnostic process.³⁸⁰ To reduce the occurrence of disease misclassification error in epidemiological studies, the use of sensitive and specific criteria for outcome ascertainment is of paramount importance.³⁸¹ In comparison to the most rigorous method for AD ascertainment, namely post-mortem neuropathologic examinations, studies have suggested that the NINCDS-ADRDA “has fair sensitivity (49-100%) and specificity (47-100%)” for the diagnosis of probable AD.²⁶ The sensitivity (85 to 96%) but not specificity (32 to 61%) indexes are said to be higher for diagnoses of possible AD.²⁶

Despite the obvious challenges associated with AD ascertainment, the potential for outcome misclassification error can be reduced by ensuring that the data used to guide the diagnostic process is as accurate as possible.³⁸² With respect to the NINCDS-ADRDA, this can be achieved by relying on experienced clinicians or personnel for the administration of the tool, incorporating brain imaging data, and further reducing subjectivity by employing a “consensus” panel decision making process.²⁶ The diagnostic assessment used to arrive at a clinical diagnosis of AD varied across the studies that employed the NINCDS-ADRDA criteria. Of particular importance, only three studies^{336, 368,371} used imaging data, albeit only for a subset of the sample (i.e. when the data was already available or deemed necessary).

Moreover, although a number^{336,343, 365, 370} of the included studies explicitly stated that the criteria was applied by a specialist or an experienced clinician, a consensus procedure to improve diagnostic accuracy was employed in only three^{365,366,371} of the included studies.

Considered cumulatively, these shortcomings indicate that the included studies are susceptible to outcome misclassification error as subjects may have been misdiagnosed. The effect of the misclassification error is dependent on whether the measurement error is associated with the exposure under study.³⁸³ If misdiagnosis of AD is unrelated to exposure status, that is, stressed and non-stressed subjects are equally likely to be misdiagnosed, outcome misclassification error would attenuate the association between stress and AD.³⁸³ Alternatively, if the outcome measurement error is related to exposure status, the observed risk estimate could either attenuate or inflate the true association.³⁸³ Ensuring that clinicians responsible for outcome ascertainment are unaware of the exposure under study or are “blind to exposure status” would mitigate the potential for outcome misclassification bias.³⁸⁴

Although all included cohort studies excluded prevalent cases of dementia at baseline, mild cases of dementia may have been missed as diagnostic screening tools may lack the ability to detect such cases.²¹ Consequently, missed cases of mild AD may be retained in longitudinal studies and may be misclassified as “incident cases at follow up”.²¹ Inclusion of prevalent cases is particularly problematic if exposure status is altered as a result of the disease.⁹³

Reliance on medical records for outcome ascertainment may also give rise to outcome measurement error.²¹ Briefly, reliance on medical records for AD ascertainment is problematic because approximately 50% of individuals with AD or dementia “are never diagnosed in a formal setting”.^{21,385} Therefore, a positive diagnosis of AD is absent from their medical records. Consequently, the study by Yaffe et al.³⁶⁷, which relied solely on medical records for AD ascertainment, is susceptible to outcome measurement error as a number of cases of AD may have been missed. Similarly, deceased participants or those lost to follow-up may have been misdiagnosed in the two^{343,365} studies that relied on medical records or death certificates for AD ascertainment in the aforementioned subset of participants. Finally, population-based studies that fail to assess the outcome of interest in all participants, often due to resource limitations, are susceptible to outcome misclassification error.²¹ Outcome misclassification error may have occurred in the Kungsholmen project³⁶⁵ and Swedish Twins study³⁶⁶ as only a fraction of subjects, namely those diagnosed with cognitive impairment based on a cognitive screening test, underwent the complete diagnostic assessment for dementia and AD. This may have resulted in missed cases due to the high rate of false negative results attributed to the “low sensitivity of screening tests”.²¹ The other studies did not appear to utilize a similar approach.

Retrospective studies examining putative risk factors for dementia and AD face several challenges pertaining to exposure ascertainment. Because subjects are required to recall exposure history, such studies are susceptible to recall bias, a form of observation bias.³⁸⁶ Retrospective studies of cognitively impaired subjects face the added challenge of ascertaining exposure status of cognitively impaired or demented cases who often lack the capacity to recall past exposures.²¹ Consequently, a proxy respondent is often recruited to provide data for the purpose of exposure ascertainment.²¹ Recall bias may arise in such studies if the ability to recall past exposures is related to the outcome under investigation, resulting in “differential recall”.^{72,387} That is, if cases (or the proxy respondents of cases) are more likely to provide an accurate depiction of exposure history when compared to controls (or the proxy respondents of controls), or vice-versa, the derived risk estimate would be biased.³⁸⁷ The susceptibility for recall bias is further heightened if methods for exposure ascertainment are not similar across outcome categories.⁷² The Swedish Twins study is susceptible to this bias as proxy respondents were responsible for ascertaining the exposure status of cases while controls reported their own exposure status.³⁶⁶ Based on the assumption that self-reported exposure history is more accurate than that provided by a proxy respondent⁷², data collected from control subjects would likely be more accurate. Consequently, differential recall is likely to have biased the association toward the null resulting in an attenuated risk estimate.^{72,388}

The study of subjective variables or constructs, such as psychological stress, can be particularly challenging as “individuals can differ...in their evaluation [and perception] of stress”.³⁴³ As previously mentioned (section 5.1), individual differences impact the appraisal of potential stressors and coping mechanisms.³⁵⁰ As a result of these differences, the interpretation of “stress” is known to vary.^{350,389} What is considered a stressful event, and the intensity at which it is experienced, may not be universal.^{350,351,389} The lack of a uniform definition of psychological stress is believed to compromise the validity of self-reported stress measures.³⁸⁹

Although the tools employed for the purpose of exposure ascertainment in the studies by Wilson et al. were derived from a psychometrically sound instrument, use of abbreviated versions of the original instrument may have compromised the “precision” of the tool, consequently giving rise to exposure measurement error which may have attenuated the association between stress and AD.³⁶⁸ Johansson et al. relied on an even more brief measure, “a single question”, to ascertain exposure status.³⁴³ Although studies have found that abbreviated tools often yield comparable results as their lengthier counterparts, some research suggests that multiple questions are typically required to yield an accurate measure of “complex psychological constructs”.³⁴¹ Consequently, the use of a single question to ascertain stress exposure may have introduced some degree of uncertainty and may serve as a limitation of the study.

The retrospective cohort study by Yaffe et al. used administrative data captured in the VA National Patient Care Database to ascertain exposure status.³⁶⁷ Although the validity of existing data sources may be compromised by “data entry errors, diagnostic inaccuracy, or various other factors...”, research suggests that the validity of administrative data, particularly pertaining to the ascertainment of PTSD among veterans, is improved when exposure ascertainment requires a positive diagnosis of PTSD at two or more medical visits.³⁹⁰ The study by Yaffe et al. adhered to this criterion; however, the authors note that reliance on ICD-9 codes captured in administrative databases lacks the diagnostic accuracy offered by alternate methods of exposure ascertainment.³⁶⁷ While validated, the psychosocial job exposure matrix used to ascertain work-related stress in both the Kungsholmen and Swedish twins study was shown to only moderately correlate with self-reported stress (average $r = 0.60$).³⁶⁵

Findings of the included studies which suggest an increased risk of AD associated with stress or stress indicators may be attributed to alternative explanations including confounding and reverse causation. Because stress is associated with several vascular and lifestyle-related risk factors for AD, including “socioeconomic status, nutritional status, smoking, hypertension, central adiposity, and physical activity”, the association between stress and AD may be confounded by these variables.³⁴³ Although all of the included studies provided adjusted risk estimates, there was heterogeneity across the included studies with respect to the variables selected for multivariate analyses and the degree of confounding adjustment. Of particular importance, all three studies by Wilson et al. failed to adjust for the potentially confounding effect of vascular risk factors and only one³⁴³ study adequately controlled for lifestyle-related factors. As such, residual confounding cannot be omitted as a potential explanation for the observed associations.

Johansson et al.³⁴³ investigated reverse causation as an explanation for the observed association between stress and AD. Psychological stress remained associated with dementia following exclusion of the earliest cases of confirmed dementia (subjects diagnosed before 1992).³⁴³ It is also important to consider that the observed association between the personality trait of neuroticism and AD may be due to reverse causation.³⁹¹ Although personality traits are relatively constant, research suggests that personality alterations may accompany cognitive decline.^{391,392} Consequently, rather than predicting AD, neuroticism may in fact be a product or symptom of undiagnosed dementia.³⁹¹ Although the potential for reverse causation is minimized in prospective studies, failure to adequately exclude preclinical cases of dementia at baseline may yield findings that are explained by reverse causation.³⁹¹ Although dementia cases were excluded at baseline in all four studies that examined neuroticism as an indicator of psychological stress, mild cases of dementia may have been missed as commonly employed diagnostic tools may lack the

sensitivity to diagnose such cases.²¹ Consequently, the observed association between neuroticism and AD may be explained by reverse causation.

The present review is limited by several factors which warrant cautious interpretation of the study findings. The review is limited by the various methodological limitations inherent in observational studies as well as the complexity associated with ascertaining both the exposure and outcome of interest.^{21,342} The review may also be limited by variability in the degree of confounding adjustment across studies.⁵⁶ The review is susceptible to study selection bias as independent, duplicate screening of all identified studies was not conducted.³⁹³ Moreover, because the review was restricted to English and French articles, the potential for language bias cannot be ruled out.³⁹⁴ Despite the limitations, the systematic review is strengthened by a comprehensive search of electronic databases, and restriction to studies employing acceptable criteria for outcome ascertainment. While grey literature sources were searched, the potential for publication bias cannot be omitted.

Several biological mechanisms have been proposed to explain the association between stress and AD. Stress and stress indicators, namely neuroticism, have been associated with hyperactivity of the hypothalamic-pituitary-adrenal axis and subsequent elevation of glucocorticoid levels which contribute to AD-related pathology.³⁴³ However, findings from autopsy examinations conducted in three^{336,369,370} of the included studies suggest that the association between proneness/vulnerability to stress and AD was not explained by histopathological hallmarks of AD, namely, amyloid beta plaques and neurofibrillary tangles.³⁷⁰ Several alternative pathways implicating the role of stress on factors associated with AD, namely, neuroinflammation, hippocampal damage, cardiovascular disease, hypertension, and obesity, have been suggested.^{343,370} PTSD has been associated with hippocampal abnormalities, such as "decreased concentrations of the neuronal marker, N-acetyl aspartate", reduced hippocampal volume, and hippocampal damage, factors associated with an increased risk of cognitive impairment and dementia.³⁶⁷ Dysfunction of the hypothalamic-pituitary-adrenal axis and increased concentrations of inflammatory markers, namely cytokines and C-reactive protein, have also been implicated as potential mechanisms to explain the increased risk of AD observed among veterans with PTSD.³⁶⁷

Results of the systematic review suggest that the available evidence was largely inadequate to suggest an association between stress (i.e. psychological, work-related) and stress indicators (i.e. PTSD, neuroticism) with risk of AD. Several limitations such as the potential for reverse causation, difficulties in defining and measuring stress, and diagnostic challenges relating to AD ascertainment preclude a definitive conclusion. As such, there is inadequate evidence to justify public health recommendations for interventions.

CHAPTER 6: CONCLUSION

6.1 SUMMARY

A comprehensive search of the literature yielded 27 systematic reviews examining 20 putative risk factors for Alzheimer's disease. While the evidence was suggestive of an association for some risk factors, the available evidence was inadequate to draw meaningful conclusions for a majority of factors. Factors that showed an association with AD included current smoking, light-to-moderate alcohol consumption, higher educational attainment, and regular engagement in physically and cognitively stimulating activities. As discussed in greater detail in Chapter 3, certain factors (i.e. higher educational attainment, physical and cognitive activity) are likely associated with postponement of clinical symptoms rather than disease prevention.^{220,223,228,249} The available evidence for the remaining factors identified in the overview of reviews was preliminary or inconclusive due to inconsistent findings or insufficient evidence.

Results of the de novo systematic review suggest that the available evidence was largely inadequate to suggest an association between stress (i.e. psychological, work-related) and stress indicators (i.e. PTSD, neuroticism) with risk of AD. With respect to the updated systematic review, the small number of available studies precludes a definitive conclusion regarding the association between Mediterranean diet adherence and risk of AD.

6.2 LIMITATIONS

The systematic synthesis of available research is an integral phase of knowledge translation, a process which aims to “[close] the knowledge-to-practice gap”.³⁹⁵ According to evidence-based practice, systematic reviews, particularly of high-quality randomized controlled trials, provide the best evidence for clinical and health policy decision making.³⁹⁶ In the absence of RCTs and reviews collating such evidence, systematic reviews of observational studies provide the next best level of evidence.³⁹⁶ The quality of systematic reviews, however, is largely dependent on a number of factors including the methodological characteristics of the review and the quality of the included studies. Risk factor- specific limitations have been discussed in their respective sections of the current report. However, several overarching issues, which limit the applicability of the findings to inform public health interventions, require further discussion.

6.2.1 Issues relating to the inclusion of existing systematic reviews

The popularity of systematic reviews is reflected in the vast number of new systematic reviews “indexed annually in Medline”.³⁹⁷ By collating the available evidence using a systematic and transparent approach, systematic reviews facilitate the transfer of available evidence.³⁹⁶ However, the rising popularity of systematic reviews has necessitated a further synthesis of the available evidence, that is, the conduct of “systematic reviews of systematic reviews”.³³ Rather than conducting a *de novo* review, research bodies such as the Agency for Healthcare Research and Quality (AHRQ) have relied on higher quality existing reviews.²⁰ While the reliance on existing reviews may expedite the review process, several limitations accompany the inclusion of existing reviews.³³ Firstly, any errors (e.g. transcription) or biases (e.g. selection or publication) may go undetected and be carried forward.³³ A majority of reviews do not describe the methodological characteristics of primary studies with sufficient detail to allow for independent assessment of bias.³³ Reliance on the review alone may result in a disregard of primary study level limitations.³³ The quality appraisal of primary studies was not planned for the overview of systematic reviews reported in Chapter 3. This may serve as an important limitation of the study.

6.2.1.1 Discordance

The complexity afforded by multiple reviews covering the same research topic is compounded by the availability of conflicting reviews. When multiple moderate or high quality reviews are identified, recommendations suggest reliance on the most methodologically superior review which is ascertained according to an assessment of “relevance, quality, and completeness”.³³ As noted by Whitlock et al., choosing one review among many is challenging and may in fact introduce “reviewer bias” in the presence of discordance.³³ Alternatively, the incorporation and summary of all existing systematic reviews has also been proposed.³³ To minimize reviewer bias and ensure that decision makers were provided with a comprehensive report of all available moderate and high quality reviews, the latter approach was selected *a priori* for the overview of reviews reported in Chapter 3. Although this approach maximized comprehensiveness, as some reviews may have captured primary studies that were excluded or undetected by another, the inclusion of multiple reviews reporting on the same risk factor introduced challenges with respect to synthesizing the available evidence in the presence of discordant findings across reviews. Conflicting findings are particularly problematic for end-users, namely, health care

workers and policy makers who are required to discern the most reliable review in which to base their decision.⁹⁰ Research has demonstrated that reliance on review quality as a potential explanation for discordant findings is inadequate as reviews of similar methodological quality may still yield conflicting results.³⁹⁸

Identifying sources of discordance is challenging and as noted by Whitlock et al., “even a detailed review of the methods and conclusions generated by existing systematic reviews may be unable to identify sources of discrepancy”.³³ In the overview of reviews (Chapter 3), discordant findings across reviews occurred often. As described throughout Chapter 3, differences in search strategies, eligibility criteria, and data extraction approaches were common sources of discordance. Based on recommendations, important methodological characteristics (i.e. clinical question, search strategy, eligibility criteria, statistical methods, etc.) of each included review were summarized to facilitate the identification of methodological discrepancies across reviews which may account for discordant findings.³³ Finally, as illustrated in Figure 1 (Section 2.2) discordant findings across reviews may indicate the need for a de novo review³³. While potential sources of discordance were explored, failure to conduct de novo systematic reviews in light of discordant findings may serve as a limitation of the study.

6.2.1.2 Overlap

A recent review sought to identify the extent to which multiple meta-analyses investigated the same interventions, populations, or outcomes were published.³⁹⁹ The reviewers found considerable overlapping meta-analyses. More specifically, an overlapping meta-analysis was available for 67% of identified meta-analyses.³⁹⁹ The inclusion of multiple systematic reviews reporting on the same risk factor introduces the potential for primary study overlap across reviews.⁵¹ In the present study, overlapping reviews were identified for 19 of the 20 risk factors reported in the overview of reviews (Chapter 3). Reliance on the same body of evidence results in the non-independence of reviews. Further, multiple reviews reporting on the same topic or clinical question results in unnecessary duplication of research efforts and waste of research resources.³⁹⁹ Extensive primary study overlap emphasizes the “redundancy” of multiple reviews examining the same research question.³⁹⁹ As recommended, the extent of primary study overlap across systematic reviews was explored and recorded in the evidence tables reported in the first phase of the study (Chapter 3).⁵¹ The transparent reporting of the extent of primary study overlap clearly communicates the number of unique studies captured by a systematic review and may also facilitate the identification of sources of discordance across reviews.

6.2.1.3 Quality Assessment

Employing an aggregate AMSTAR quality score serves as a limitation of the overview of reviews.^{51,400} The approach employed by CADTH, which was adopted for the present study, disregards the lack of weighting of each AMSTAR item.⁴⁰⁰ The use of an aggregate score is particularly problematic as reviews with a substantial limitation may still receive a high quality score if other considered items are adequately satisfied.⁵¹ Moreover, the distribution of scores may differ for reviews of the same quality category.⁵¹ For example, two moderate quality reviews may have “different flaws”.⁵¹ While the aggregate scoring system was employed for the overview of reviews, the distribution of scores for each study were transparently reported (Appendix A-6). Finally, like other quality appraisal instruments, AMSTAR assesses quality of reporting rather than true methodological quality.⁴⁰⁰ This issue was discussed in further detail in the overview of reviews reporting on folate exposure (Section 3.5).

6.2.1.4 Publication bias

Primary studies reporting null or negative findings may be less likely to be published.⁴³ Likewise, authors investigating several risk factors may choose to omit null findings from published manuscripts.²⁰ Because the presence of publication bias may pose threats to the validity of a systematic review, an initiative to facilitate the identification of unpublished or incompletely published primary studies has been recommended.²⁰ The development of a registration system for cohort studies, which would require a priori declaration of intended analyses, may circumvent incomplete reporting of study findings.²⁰ Such a registry would also aid in locating studies that have not been published.

In the overview of reviews study, less than 50% of reviews assessed the likelihood of publication bias. Systematic reviewers should be encouraged, where data permits, to examine the extent to which their findings may be explained by publication bias. The development of quality assessment tools such as AMSTAR, which reward the assessment of publication bias, may serve as a motivation to do so.

6.2.2 Observational study limitations

This report synthesized evidence from observational studies and systematic reviews of observational studies. Reliance on observational studies warrants a cautious interpretation of the results. Of particular importance, results of observational studies do not infer causality.³⁷ Moreover, observational studies are susceptible to several sources of bias. Studies that assess exposures retrospectively are susceptible to recall error. If the ability to recall past exposures is related to the outcome of interest, exposure measurement bias may arise.^{72,326} This is particularly problematic in dementia research as the disease process directly effects memory function and consequently, recall accuracy.²¹¹ Case-control studies should ensure that methods for exposure ascertainment are similar across outcome categories.⁷² In cohort studies, ensuring that prevalent cases (i.e. cognitively impaired subjects) are adequately detected and excluded at baseline is integral for mitigating the potential for both differential recall bias and reverse causation.^{21,272} Reverse causation may account for the observed associations as AD-related cognitive changes may impact exposure status.⁹³ For example, engagement in physical and cognitive activities may decline as a result of cognitive impairment.^{267,272} Inclusion of subjects with cognitive deficits at baseline, as a result of failing to assess cognitive status or due to reliance on insensitive screening measures, may yield spurious results suggesting that lower engagement in activities is associated with risk of developing AD.^{21,93,391} The cohort should be free of cognitive deficits at baseline.²¹ Alternatively, sensitivity analyses excluding such cases may be explored.²¹¹ Finally, selection bias may pose as a threat to the internal validity of observational studies. The association between the exposure and outcome of interest may differ among participants who enroll or remain in a study as compared to those who refuse participation or are lost to follow-up.^{94,95}

6.2.2.1 Exposure ascertainment

Issues relating to exposure ascertainment require considerable consideration. As discussed in the literature, large cohort studies often investigate the association between several exposures with risk of developing AD.²⁰ To do so, each exposure is ascertained according to brief, self-reported measures which often have not been validated.²⁰ A consistently cited limitation across primary studies seeking to examine the association between lifestyle risk factors and risk of AD relates to the accuracy of exposure ascertainment.²⁰ Limitations related to self-report data, in particular, have underscored the need for

objective measures as a means to replace or corroborate self-reported data.^{20,144} The need for standardized approaches for exposure ascertainment has also been cited.²⁰ To facilitate this, the development of a database which includes a list of “reliable and valid” exposure measurement tools has been proposed.²⁰ Such a database would encourage researchers to rely on validated measures and would also facilitate homogeneity across studies.²⁰

A particular concern in AD risk factor research pertains to the appropriate timing of exposure ascertainment.²⁰ The neuropathological changes associated with AD have been detected as early as the second decade of life.¹⁸ Research suggests that cognitive decline may precede clinically overt AD by approximately one decade.²⁰ As noted by Williams et al.²⁰, many cohort studies examine exposures after midlife when it is likely that cognitive changes have already manifested. Such studies are likely to have “missed the critical window of exposure”, a theory which posits that particular exposures are capable of exhibiting a deleterious or protective effect during a specific window of time.²⁰ For example, the primary studies identified in the updated review on Mediterranean diet adherence ascertained exposure in late-life (Chapter 4). Because subjects in both studies were over 75 years of age at baseline, these studies provide no insight on the effect of Mediterranean diet adherence during early and midlife on risk of AD in late-life. Ascertaining the effect of exposures, such as the Mediterranean diet, across the life course may identify critical exposure windows allowing for more effective interventions.²⁰ Further research should also attempt to ascertain whether exposures exert a cumulative effect over time.

To minimize the potential for reverse causation, studies must examine exposures early enough to precede disease onset.²¹ As pathophysiological changes begin decades prior to clinically confirmed AD, studies which ascertain exposure status in later-life are susceptible to reverse causation.²¹ That is, a putative factor may be a consequence rather than a cause of AD. This is a common issue across studies of aging as they most often recruit subjects in later-life (i.e. age 65 and over).²¹ Studies which ascertain exposure status in earlier life and follow subjects over a longer duration of time are ideal.²¹ Although ensuring that exposure ascertainment occurs early enough to precede disease onset is imperative for providing evidence that is suggestive of causality, there is also merit in the measurement of exposures after the initiation of pathophysiological changes and symptom onset as they may continue to exhibit an effect with respect to disease progression.^{20,21}

6.2.2.2 Outcome ascertainment

All primary studies identified in the de novo and updated reviews relied on accepted clinical diagnostic criteria. As mentioned by Williams et al.²⁰, restricting eligibility to studies that employ such criteria does not entirely eliminate heterogeneity across studies with respect to outcome ascertainment. More specifically, studies may lack methodological uniformity with respect to the diagnostic workup used to guide outcome ascertainment. As discussed in the de novo systematic review (Chapter 5), the diagnostic assessment varied across studies which relied on the NINCDS-ADRDA or similar criteria. For example, only three of eight studies employed a consensus panel decision making process and three studies considered imaging data during the diagnostic work-up. Only one of the eight studies explicitly considered information gathered from close informant interviews.

Population-based studies that fail to assess the outcome of interest in all participants, often due to resource limitations, are susceptible to outcome misclassification error.²¹ Outcome misclassification error may occur if only a fraction of subjects, namely those diagnosed with cognitive impairment based on a cognitive screening test, undergo the complete diagnostic assessment for dementia and AD. This may result in missed cases due to the high rate of false negative results attributed to the “low sensitivity of screening tests”.²¹ Implications regarding shifts in diagnostic perspectives are also worth noting.

Vascular disease and AD: Shifts in Diagnostic Perspective and Use of Brain Imaging

Historically, AD and VaD were perceived to be distinct diseases.¹⁹ This is reflected in the NINCDS-ADRDA criteria established in 1984 which requires exclusion of vascular disease (e.g. multi-infarct dementia) as a potential explanation for clinical symptoms.^{24,380} Similarly, the widely used International Workshop of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences criteria (NINDS-AIREN) for VaD shares this exclusionary approach by requiring elimination of AD as a cause of dementia.²⁴ Both criteria attempt to identify “pure” cases of AD and VaD, accordingly.²⁴ The traditional approach of excluding vascular disease in the diagnosis of AD has posed important implications in the search for etiological factors.¹⁹ The exclusion of vascular disease has implied that vascular factors are unrelated to the disease process.¹⁹ However, advancements in AD research have revealed a potential association between vascular factors and AD.^{19,401} This shift is particularly important when considering evidence from primary studies conducted over a relatively long duration of time (>20 years). There has also been a shift away from the “distinct entities” perspective towards acknowledgement of mixed

patterns of dementia.¹⁹ This is reflected in the revised NINCDS-ADRDA criteria, which has explicitly incorporated mixed dementia (e.g. AD dementia with evidence of cerebrovascular disease) as a criterion for possible AD.²⁹

Brain imaging is the gold standard for ruling out cerebrovascular disease as a cause of dementia and thereby distinguishing AD from both VaD and mixed AD-VaD.²⁴ Studies which fail to rely on neuroimaging may potentially misdiagnose VaD or mixed dementia as AD.¹⁹ As the outcome of interest in this work was AD, systematic reviews and primary studies reporting solely on dementia subtypes or mixed dementia syndromes were excluded. However, eligibility was not restricted to studies which relied on neuroimaging data to adequately distinguish “pure” AD from dementia subtypes or mixed dementia. A large majority of studies reviewed in this work relied on the 1984 version of the NINCDS-ADRDA criteria. While discussed in both versions of the NINCDS-ADRDA criteria, brain imaging has not been consistently used in research studies.¹⁹ As such, primary studies captured in the existing, de novo, and updated systematic reviews are likely heterogeneous with respect to the use of neuroimaging and thus the rigour at which AD is distinguished from VaD and mixed dementia. With respect to the de novo and updated systematic reviews, few primary studies reported the incorporation of brain imaging data in the diagnostic process. Even among these studies, neuroimaging results were only considered when available or when deemed necessary.

Advancements in imaging technology and changes in practice over time must also be considered, particularly with respect to the overview of systematic reviews which synthesizes evidence from primary studies published over a duration of two decades (Chapter 3).^{29,402} In particular, there has been a shift in the role of neuroimaging in the diagnostic process.⁴⁰² More specifically, “modern neuroimaging extends beyond [the] traditional role of excluding other conditions...and is now an essential part of AD diagnosis”.⁴⁰²

6.3 RECOMMENDATIONS AND FUTURE DIRECTIONS

The present study was done in consort with the National Population Health Study of Neurological Conditions, which aimed to “fill gaps in knowledge” regarding neurological conditions.⁴⁰³ Few factors showed a consistent association with risk of AD. While there was some evidence of an association between current smoking, low to moderate alcohol consumption, higher educational attainment, and engagement in cognitively and physically stimulating activities with risk of AD, the evidence is limited

by several methodological issues. Further, the evidence does not robustly inform the quantity, duration, or intensity that may be associated with the greatest benefit or harm. Conflicting or insufficient evidence as well as several methodological limitations preclude a conclusive statement regarding the association between AD and the remaining lifestyle factors. As the evidence base was comprised solely of observational studies yielding weak or moderate risk estimates at best, the quality of evidence was deemed “low” for each risk factor according to the GRADE approach.⁵⁴ The available evidence for Mediterranean diet adherence, psychological stress, and the risk factors examined in the overview of reviews was not robust enough to warrant an increase in the overall grade of evidence according to the criteria presented in section 2.5. The limited evidence precludes the development of public health recommendations to guide the development of preventative interventions. This conclusion is consistent with that of a recent HTA²⁰.

Several issues were identified with respect to the available literature. Of particular concern is the voluminous amount of literature which may present challenges with respect to end-user uptake. While systematic reviews aim to facilitate the uptake of evidence by synthesizing primary evidence into a more manageable format, as discussed previously, the exponential growth in the number of systematic reviews available has also proven problematic.^{397,399} Furthermore, ensuring that traditional systematic reviews are up-to-date is time consuming and resource intensive.⁴⁰⁴ A more efficient approach for providing clinicians and health care policy decision-makers with up-to-date, comprehensive, and synthesized evidence is afforded by recent initiatives such as AlzGene⁴⁰⁵ and AlzRisk⁴⁰⁶. These publically available databases systematically identify and collate high-quality, peer-reviewed primary studies on genetic and non-genetic risk factors for AD.^{405,406} The search strategies are regularly updated to identify recently published evidence. Data from eligible studies are extracted and presented qualitatively and quantitatively (if data permits).^{405,406} Ultimately, it is expected that these centralized databases will facilitate and expedite the knowledge translation process. These easily accessible portals provide end-users with synthesized and up-to-date evidence allowing for efficient decision-making. While these “field synopsis”⁴⁰⁵ databases present a novel approach for knowledge synthesis, they are unlikely to replace traditional peer-reviewed, published systematic reviews. This highlights the need for and utility of systematic review registries which serve to minimize duplication of existing reviews and act as a repository for completed and in-progress reviews.⁴⁰⁷ A centralized registry would ultimately avoid the waste of research resources and would allow for the efficient identification of reviews on a given clinical question by end-users, ultimately facilitating the knowledge translation process.^{399,407} A concerted effort is required to maximize the utility of such registries. Thus, systematic reviewers should be encouraged to register their reviews in platforms such as PROSPERO.^{399,407,408}

Several recommendations have been proposed in an effort to improve AD risk factor research at the primary study level. The need for objective, standardized, and validated exposure measures have been emphasized.²⁰ As previously discussed, knowledge synthesis activities would likely benefit from the development of observational study registries.²⁰ Such registries would facilitate the location of cohort studies and would encourage the transparent reporting of primary study findings.²⁰ Ensuring that exposure status is ascertained early enough in the lifecourse to precede pathophysiological changes associated with AD has also been proposed.²¹

Overall, while this report was able to synthesize the available evidence on lifestyle risk factors associated with AD, further research, by way of randomized controlled trials (where applicable) or methodologically “rigorous observational studies”, is required prior to developing recommendations for public health interventions or strategies.²⁰ While adherence to healthy lifestyle practices are generally conducive to improved health and chronic disease prevention, this report does not provide justification for primary prevention initiatives for AD.

REFERENCES

1. Lindsay, J and L Anderson, "Dementia and Alzheimer's Disease." Women's Health Surveillance Report, 9 Dec 2003, Public Health Agency of Canada, 10 May 2011. <http://www.phac-aspc.gc.ca/publicat/whsr-rssf/chap_19-eng.php>.
2. Strock, M. *Alzheimers Disease: Diagnosis, Cause & Treatment*. S.l.: Diane Pub Co, 1996.
3. Swerdlow, RH. "Is aging part of Alzheimer's disease, or is Alzheimer's disease part of aging?" *Neurobiology of Aging* 28.10 (2007): 1465-80.
4. *American Psychiatric Association Practice Guidelines for the Treatment of Psychiatric Disorders*. Arlington, Virg: American Psychiatric Association. 2006.
5. "Chapter 3: The Health and Well-being of Canadian Seniors." The Chief Public Health Officer's Report on The State of Public Health in Canada 2010. 28 Oct 2010. Public Health Agency of Canada. 10 May 2011. <<http://www.phac-aspc.gc.ca/cphorsphc-respcacsp/2010/fr-rc/cphorsphc-respcacsp-06-eng.php>>.
6. National Advisory Council on Aging (Canada). "The NACA position on Alzheimer disease and related dementias." 2004. 16 Feb 2011, <http://books2.scholarsportal.info/viewdoc.html?id=/ebooks/ebooks1/gibson_chrc/2010-08-06/1/10089389>.
7. Parihar, MS, and T Hemnani. "Alzheimer's disease pathogenesis and therapeutic interventions." *Journal of Clinical Neuroscience* 11.5 (2004): 456-67.
8. Gauthier, S, Y Wirth, and HJ Mobius. "Effects of memantine on behavioural symptoms in Alzheimer's disease patients: an analysis of the Neuropsychiatric Inventory (NPI) data of two randomised, controlled studies." *International Journal of Geriatric Psychiatry* 20.5 (2005): 459-64.
9. Aglukkaq, L. "Alzheimer's Awareness Month: January 2011." 04 Jan 2011. Health Canada, 16 Feb 2011, <http://www.hc-sc.gc.ca/ahc-asc/minist/messages/_2011/2011_01_04-eng.php>.
10. Mayeux, R, and Y Stern. "Epidemiology of Alzheimer disease." *Cold Spring Harbor Perspectives in Medicine* 2 (2012).

-
11. Alzheimer Society, "Rising Tide: The Impact of Dementia on Canadian Society." 2010. 06 June 2012.
<http://www.alzheimer.ca/~media/Files/national/Advocacy/ASC_Rising%20Tide-Executive%20Summary_Eng.ashx>.
 - 12."Alzheimer's Disease." Health Research - Investing in Canada's Future 2004-2005. 23 Nov 2006. Canadian Institutes of Health Research. Feb 2011. <<http://www.cihr-irsc.gc.ca/e/28891.html>>.
 - 13.Braak, H, and E Braak."Neuropathological staging of Alzheimer-related changes."Acta Neuropathologica 82.4 (1991): 239-59.
 14. Ballard, C, S Gauthier, A Corbett, C Brayne, D Aarsland, and E Jones. "Alzheimer's disease." Lancet 377.9770 (2011): 1019-31.
 - 15.Schapira, AHV. *Neurology and Clinical Neuroscience: Chapter 65: Alzheimer's disease* (Philadelphia, Mosby/Elsevier, 2007) 848-9.
 16. Moreira, PI, C Carvalho, X Zhu, MA Smith, and G Perry. "Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology." Biochimica et Biophysica Acta 1.1802 (2010): 2-10.
 17. Jack, CR, MS Albert, DS Knopman, GM McKhann, RA Sperling, MC Carillo, B Thies, and CH Phelps.
"Introduction to the recommendations from the National Institute on Aging and the Alzheimer's Association workgroup on diagnostic guidelines for Alzheimer's disease." Alzheimer's & Dementia 7.3 (2011): 257-62.
 - 18.Borenstein, AR, CI Copenhaver, and JA Mortimer."Early-life risk factors for Alzheimer disease." Alzheimer Disease and Associated Disorders 20.1 (2006): 63-72.
 19. Stewart, R. "Vascular dementia: a diagnosis running out of time." The British Journal of Psychiatry 180 (2002): 152-6.
 - 20.Williams, JW, BL Plassman, J Burke, and S Benjamin."Preventing Alzheimer's Disease and Cognitive Decline."Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.)AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.
 - 21.van der Flier, WM, and P Scheltens. "Epidemiology and risk factors of dementia." Journal of Neurology, Neurosurgery, and Psychiatry 76 (Suppl V) (2005): v2-7.

-
22. Dubois, B, HH Feldman, C Jacova, ST Dekosky, P Barberger-Gateau, J Cummings, A Delacourte, D Galasko, S Gauthier, G Jicha, K Meguro, J O'brien, F Pasquier, P Robert, M Rossor, S Salloway, Y Stern, PJ Visser, and P Scheltens. "Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria." *Lancet Neurology* 6.8 (2007): 734-46.
23. Reisberg, B. "Diagnostic criteria in dementia: a comparison of current criteria, research challenges, and implications for DSM-V." *Journal of Geriatric Psychiatry & Neurology* 19.3 (2006): 137-46.
24. Gauthier, S. *Clinical Diagnosis and Management of Alzheimer's Disease*. Scarborough: Taylor and Francis, 2000.
25. Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 282.
26. Biessels, GJ, S Staekenborg, E Brunner, C Brayne, and P Scheltens. "Risk of dementia in diabetes mellitus: a systematic review." *Lancet Neurology* 5.1 (2006): 64-74.
27. Jayakar, JP, and J Huang. "Alzheimer's disease: a review of diagnostic criteria." *UWOMJ* 79.2 (2010).
28. Wattamwar, PR, and PS Mathuranath. "An overview of biomarkers in Alzheimer's disease." *Annals of Indian Academy of Neurology* 13.2 (2010): S116-23.
29. McKhann, GM, DS Knopman, H Chertkow, BT Hyman, CR Jack, CH Kawas, WE Klunk, WJ Koroshetz, JJ Manly, R Mayeux, RC Mohs, JC Morris, MN Rossor, P Scheltens, MC Caririllo, B Thies, S Weintraub, and CH Phelps. "The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." *Alzheimer's and Dementia* 7.3 (2011): 263-9.
30. Hyman, BT, CH Phelps, TG Beach, EH Bigio, NJ Cairns, MC Carrillo, DW Dickson, C Duyckaerts, MP Frosch, E Masliah, SS Mirra, PT Nelson, JA Schneider, DR Thal, B Thies, JQ Trojanowski, HV Vinters, and TJ Montine. "National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease." *Alzheimer's and Dementia* 8.1 (2012): 1-13.
31. Beach, TG, SE Monsell, LE Phillips, and W Kukull. "Accuracy of the clinical diagnosis of Alzheimer disease at the National Institute on Aging Alzheimer's Disease Centers, 2005-2010." *Journal of Neuropathology and Experimental Neurology* 71.4 (2012): 266-73.

-
32. Markesbery, WR. "Neuropathological criteria for the diagnosis of Alzheimer's disease." *Neurobiology of Aging* 18.S4 (1997): S13-19.
33. Whitlock, EP, JS Lin, R Chou, P Shekelle, and KA Robinson. "Using existing systematic reviews in complex systematic reviews." *Annals of Internal Medicine* 148.10 (2008): 776-82.
34. Bassil, N, and GT Grossberg. "Evidence-based Approaches to Preventing Alzheimer's Disease, Part 1." *Primary Psychiatry* 16.6 (2009): 29-37.
35. Clevenger, CK, S Cantey, and ME Quinn. "Teaching Primary Prevention of Alzheimer's Disease: Does It Make a Difference?" *Journal of Primary Care and Community Health* 1.2 (2010): 134-8.
36. Barnes, DR, and K Yaffe. "The projected effect of risk factor reduction on Alzheimer's disease prevalence." *Lancet Neurology* 10 (2011): 819-828.
37. Viswanathan, M, AM Siega-Riz, MK Moos, A Deierlein, S Mumford, J Knaack, P Thieda, LJ Lux, and KN Lohr. "Outcomes of maternal weight gain." *Evidence Report Technology Assessment* 168 (2008): 1-223.
38. Rosdahl, CB, and MT Kowalski. *Textbook of Basic Nursing*. Philadelphia: Lippincott Williams & Wilkins, 2008. Print.
39. Appel, LJ, MW Brands, SR Daniels, N Karanja, PJ Elmer, and FM Sacks. "Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association." *Hypertension* 47.2 (2006): 296-308.
40. Huai, P, H Xun, KH Reilly, Y Wang, W Ma, and B Xi. "Physical activity and risk of hypertension: a meta-analysis of prospective cohort studies." *Hypertension* 62 (2013).
41. Colberg, SR, RJ Sigal, B Fernhall, JG Regensteiner, BJ Blissmer, RR Rubin, L Chasan-Taber, AL Albright, and B Braun. "Exercise and type 2 diabetes." *Diabetes Care* 33.12 (2010): e147-67.
42. Stern, C, and Z Munn. "Cognitive leisure activities and their role in preventing dementia: a systematic review." *International Journal of Evidence Based Healthcare* 8.1 (2010): 2-17."
43. Dubben, HH, and HP Beck-Bornholdt. "Systematic review of publication bias in studies on publication bias." *British Medical Journal* 331 (2005).
44. Okoli, C, and K Schabram. "A Guide to Conducting a Systematic Literature Review of Information Systems Research." *Sprouts: Working Papers Information Systems* 10.26 (2010).

-
45. Moher, D, and A Tsertsvadze. "Systematic reviews: when is an update an update?" *Lancet* 367.9514 (2006): 881-3.
46. Young, MM, A Stevens, A Porath-Waller, T Pirie, C Garritty, B Skidmore, L Turner, C Arratoon, N Haley, K Leslie, R Reardon, B Sproule, J Grimshaw, and D Moher. "Effectiveness of brief interventions as part of the screening, brief intervention and referral to treatment (SBIRT) model for reducing the non-medical use of psychoactive substances: a systematic review protocol." *Systematic Reviews* 1.22 (2012).
47. Higgins, J, and J Deeks. "Chapter 7: Selecting studies and data collection." *The Cochrane Collaboration*. 2008. Web. 14 May 2011 <http://www.igh.org/Cochrane/tools/Ch07_Collecting.pdf>.
48. Landis, JR, and GG Koch. "The measurement of observer agreement for categorical data." *Biometrics* 33.1 (1977): 159-74.
49. Shea, BJ, C Hamel, GA Wells, LM Bouter, E Kristjansson, J Grimshaw, DA Henry, and M Boers. "AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews." *Journal of Clinical Epidemiology* 62.10 (2009): 1013-20.
50. "Rx for Change: Methods for Development." *CADTH - Canadian Agency for Drugs and Technologies in Health*. Web. 23 June 2011 <<http://www.cadth.ca/resources/rx-for-change/methods-for-development>>.
51. White, CM, S Ip, M McPheeters, TS Carey, R Chou, KN Lohr, K Robinson, K McDonald, and E Whitlock. "Using existing systematic reviews to replace de novo processes in conducting comparative effectiveness reviews." *AHRQ Methods for Effective Health Care* (2009).
52. Braga, LH, J Pemberton, J Demaria, and AJ Lorenzo. "Methodological concerns and quality appraisal of contemporary systematic reviews and meta-analyses in pediatric urology." *Journal of Urology* 186.1 (2011): 266-72.
53. Takwoingi, Y, S Hopewell, and D Tovey. "A multicomponent decision tool for prioritising the updating of systematic reviews." *British Medical Journal* 347 (2013).
54. GRADE Working Group. "Grading quality of evidence and strength of recommendations." *British Medical Journal* 328.7454 (2004).

-
55. Daviglus, ML, BL Plassman, A Pirzada, CC Bell, PE Bowen, JR Burke, ES Connelly Jr, JM Dunbar-Jacob, EC Granieri, K McGarry, D Patel, M Trevisan, and JW Williams Jr. "Risk factors and preventive interventions for Alzheimer disease: state of the science." *Archives of Neurology* 68.9 (2011): 1185-90.
56. Peters, R, J Peters, J Warner, N Beckett, and C Bulpitt. "Alcohol, dementia and cognitive decline in the elderly: a systematic review." *Age & Ageing* 37.5 (2008): 505-12.
57. Anstey, KJ, HA Mack, and N Cherbuin. "Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies." *American Journal of Geriatric Psychiatry* 17.7 (2009): 542 – 555.
58. Standridge, JB. "Pharmacotherapeutic Approaches to the Prevention of Alzheimer's Disease." *The American Journal of Geriatric Pharmacotherapy* 2.2 (2004): 119-132.
59. Purnell, C, S Gao, CM Callahan, and HC Hendrie. "Cardiovascular Risk Factors and Incident Alzheimer's Disease: A Systematic Review of the Literature." *Alzheimer Disease and Associated Disorders* 23.1 (2009): 1-10.
60. The ESHRE Capri Workshop Group. "Perimenopausal risk factors and future health." *Human Reproduction Update* 17.5 (2011): 706 – 717.
61. Graves, AB, CM van Duijn, V Chandra, L Fratiglioni, A Heyman, AF Jorm, E Kokmen, K Kondo, JA Mortimer, WA Rocco, et al. "Alcohol and tobacco consumption as risk factors for Alzheimer's disease: a collaborative re-analysis of case-control studies." *International Journal of Epidemiology* 20.2 Suppl 2 (1991): S48-S56.
62. Weih, M, J Wiltfang, and J Kornhuber. "Non-pharmacologic prevention of Alzheimer's disease: nutritional and life-style risk factors." *Journal of Neural Transmission* 114.9 (2007): 1187-1197.
63. Patterson, C, J Feightner, A Garcia, and C MacKnight. "General risk factors for dementia: A systematic evidence review." *Alzheimer's and Dementia* 3.4 (2007): 341-7.
64. Lee, Y, JH Back, J Kim, SH Kim, DL Na, HK Cheong, CH Hong, and YG Kim. "Systematic review of health behaviour risks and cognitive health in older adults." *International Psychogeriatrics* 22.2 (2010): 174-187.
65. van Duijn, CM, et al. "Risk factors for Alzheimer's disease: overview of the EURODEM collaborative re-analysis of case-control studies." *International Journal of Epidemiology* 20.2 Suppl 2 (1991): S4-S12.

-
66. Hofman, A, et al. "History of dementia and Parkinson's disease in first degree relatives of patients with Alzheimer's disease." *Neurology* 39.12 (1989): 1589-92.
67. Heyman, A, WE Wilkinson, JA Stafford, MJ Helms, AH Sigmon, and T Weinberg. "Alzheimer's disease: A study of epidemiological aspects." *Annals of Neurology* 15.4 (1984): 335-41.
68. Kokmen, E, CM Beard, V Chandra, KP Offord, BS Schoenberg, and DJ Ballard. "Clinical risk factors for Alzheimer's disease: A population-based case-control study." *Neurology* 41.9 (1991): 1393-7.
69. Amaducci, LA, L Fratiglioni, WA Rocca, C Fieschi, P Livrea, D Pedone, L Bracco, A Lippi, C Gandolfo, and G Bino. "Risk factors for clinically diagnosed Alzheimer's disease: A case-control study of an Italian population." *Neurology* 36.7 (1986): 992-31.
70. Chandra, V, V Philipose, PA Bell, A Lazaroff, and BS Schoenberg. "Case-control study of late onset 'probable Alzheimer's disease'." *Neurology* 37.8 (1987): 1630-33.
71. Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 271, 364.
72. Hassan, E. "Recall Bias can be a Threat to Retrospective and Prospective Research Designs." *The Internet Journal of Epidemiology* 3.2 (2006).
73. dos Santos Silva, I. "Chapter 9: Case-control studies." *Cancer Epidemiology: Principles and Methods*. Lyon: International Agency for Research on Cancer. 1999. <<http://www.iarc.fr/en/publications/pdfs-online/epi/cancerepi/CancerEpi-0.pdf>>. Web. 14 Oct. 2012.
74. Yoshitake, T, Y Kiyohara, I Kato, T Ohmura, H Iwamoto, K Nakayama, S Ohmori, K Nomiyama, H Kawano, K Ueda, et al. "Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama study." *Neurology* 45.6 (1995) 1161-8.
75. Orgogozo, JM, JF Dartigues, S Lafont, L Letenneur, D Commenges, R Salamon, S Renaud, and MB Breteler. "Wine consumption and dementia in the elderly: a prospective community study in the Bordeaux area." *Rev Neurol* 153.3 (1997): 185-92.
76. Lindsay, J, D Laurin, R Verreault, R Hebert, B Helliwell, GB Hill, and I McDowell. "Risk factors for AD: a prospective analysis from the Canadian Study of Health and Aging." *American Journal of Epidemiology* 156.5 (2002): 445-53.

-
77. Ruitenberg, A, JC van Swieten, JC Witteman, KM Mehta, CM van Duijn, A Hofman, and MM Breteler. "Alcohol consumption and risk of dementia: the Rotterdam study." *Lancet* 359.9303 (2002): 281–6.
78. Truelsen, T, D Thudium, and M Gronbaek. "Amount and type of alcohol and risk of dementia: the Copenhagen City Heart Study." *Neurology* 59.9 (2002): 1313–19.
79. Mukamal, K, LH Kuller, AL Fitzpatrick, WT Longstreth Jr., MA Mittleman, and DS Siscovick. "Prospective study of alcohol consumption and risk of dementia in older adults." *Journal of the American Medical Association* 289.11 (2003): 1405–13.
80. Luchsinger, JA, MX Tang, M Siddiqui, S Shea, and R Mayeux. "Alcohol intake and risk of dementia." *Journal of the American Geriatric Society* 52.4 (2004): 540–6.
81. Anttila, T, EL Helkala, M Viitanen, I Kareholt, L Fratiglioni, B Winblad, H Soininen, J Tuomilehto, A Nissinen, and M Kivipelto. "Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population based study." *British Medical Journal* 329.7465 (2004): 539.
82. Larrieu, S, L Letenneur, C Helmer, JF Dartigues, and P Barberger-Gateau. "Nutritional factors and risk of incident dementia in the PAQUID longitudinal cohort." *Journal of Nutrition, Health, and Aging* 8.3 (2004): 150–4.
83. Kmet, LM, RC Lee, and LS Cook. "Standard quality assessment criteria for evaluating primary research papers from a variety of fields." *Alberta Heritage Foundation for Medical Research* 2004, <www.ahfmr.ab.ca>.
84. Leibovici, D, K Ritchie, B Ledesert, and J Touchon. "The effects of wine and tobacco consumption on cognitive performance in the elderly: a longitudinal study of relative risk." *International Journal of Epidemiology* 28.1 (1999): 77–81.
85. Huang, W, C Qiu, B Winblad, and L Fratiglioni. "Alcohol consumption and incidence of dementia in a community sample aged 75 years and older." *Journal of Clinical Epidemiology* 55.10 (2002): 959–64.
86. Kivipelto, M, EL Helkala, MP Laakso, T Hanninen, M Hallikainen, K Alhainen, H Soininen, J Tuomilehto, and A Nissinen. "Midlife vascular risk factors and AD in later life: longitudinal, population based study." *British Medical Journal* 322.7300 (2001): 1447–51.
87. Deng, J, DH Zhou, J Li, YJ Wang, C Gao, and M Chen. "A 2-year follow-up study of alcohol consumption and risk of dementia." *Clinical Neurology and Neurosurgery* 108.4 (2006): 378–83

-
88. Shin, IS, R Stewart, JM Kim, SW Kim, SJ Yang, HY Shin, JS Jung, and JS Yoon. "Mitochondrial aldehyde dehydrogenase polymorphism is not associated with incidence of Alzheimer's disease." *International Journal of Geriatric Psychiatry* 20.11 (2005): 1075–80.
89. Dai, Q, AR Borenstein, Y Wu, JC Jackson, and EB Larson. "Fruit and vegetable juices and Alzheimer's disease: the Kame Project." *American Journal of Medicine* 119.9 (2006): 751-9.
90. Jadad, AR, DJ Cook, and GP Browman. "A guide to interpreting discordant systematic reviews." *Canadian Medical Association Journal* 156.10 (1997): 1411-6.
91. Higgins, J, and Sally Green. "Cochrane Handbook for Systematic Reviews of Interventions: Strategies for addressing heterogeneity." Web. March 2011. Jan. 2013.
<http://handbook.cochrane.org/chapter_9/9_5_3_strategies_for_addressing_heterogeneity.htm>.
92. Spencer, JPE, MM Abd El Mohsen, AM Minihaan, and JC Mathers. "Biomarkers of the intake of dietary polyphenols: strengths, limitations and application in nutrition research." *British Journal of Nutrition* 99.1 (2008): 12-22.
93. Bowling, A, and S Ebrahim. *Handbook of Health Research Methods: Investigation, Measurement and Analysis*. (Maidenhead: Open University Press, 2005).
94. Dettori, JR. "Loss to follow-up." *Evidence Based Spine-Care Journal* 2.1 (2011): 7-10.
95. Kawas, CH. "Diet and the risk for Alzheimer's disease." *Annals of Neurology* 59.6 (2006): 877-79.
96. Almeida, OP, GK Hulse, D Lawrence, and L Flicker. "Smoking as a risk factor for Alzheimer's disease: contrasting evidence from a systematic review of case-control and cohort studies." *Addiction* 97.1 (2002): 15-28.
97. Anstey, KJ, C von Sanden, A Salim, and R O'Kearney. "Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies." *American Journal of Epidemiology* 166.4 (2007): 367-78.
98. Cataldo, JK, JJ Prochaska, and SA Glantz. "Cigarette Smoking is a Risk Factor for Alzheimer's Disease: An Analysis Controlling for Tobacco Industry Affiliation." *Journal of Alzheimer's disease* 19.2 (2010): 465 - 480.

-
99. Peters, R, R Poulter, J Warner, N Beckett, L Burch, and C Bulpitt. "Smoking, dementia and cognitive decline in the elderly, a systematic review." *BMC Geriatrics* 8.36 (2008).
100. Graves, AB, E White, TD Koepsell, BV Reifler, G van Belle, EB Larson, and M Raskind. "A case-control study of Alzheimer's disease." *Annals of Neurology* 28.6 (1990): 766-74.
101. Broe, GA, AS Henderson, H Creasey, E McCusker, AE Korten, AF Jorm, W Longley, and JC Anthony. "A case-control study of Alzheimer's disease in Australia." *Neurology* 40.11 (1990): 1698-1707.
102. French, LR, LM Schuman, JA Mortimer, JT Hutton, RA Boatman, and B Christians. "A case-control study of dementia of the Alzheimer type." *American Journal of Epidemiology* 121.3 (1985): 414-21.
103. Shalat, SL, B Seltzer, C Pidcock, and EL Baker, Jr. "Risk factors for Alzheimer's disease: a case-control study." *Neurology* 37.10 (1987): 1630-33.
104. Barclay, L, and S Kheifets. "Tobacco use in Alzheimer's disease." *Progress in Clinical and Biological Research* 317 (1989): 189-94.
105. Brenner, DE, WA Kukull, G van Belle, JD Bowen, WC McCormick, L Teri, and EB Larson. "Relationship between cigarette smoking and Alzheimer's disease in a population-based case-control study." *Neurology* 43.2 (1993): 293-300.
106. Ferini-Strambi, L, S Smirne, P Garancini, P Pinto, and M Franceschi. "Clinical and epidemiological aspects of Alzheimer's disease with presenile onset: a case-control study." *Neuroepidemiology* 9.1 (1990): 39-49.
107. Forster, DP, AJ Newens, DW Kay, and JA Edwardson. "Risk factors in clinically diagnosed presenile dementia of the Alzheimer type: a case-control study in northern England." *Journal of Epidemiology and Community Health* 49.3 (1995): 253-8.
108. Grossberg, GT, R Nakra, V Woodward, and T Russell. "Smoking as a risk factor for Alzheimer's disease." *Journal of the American Geriatrics Society* 37.8 (1989): 819.
109. Lerner, A, E Koss, S Debanne, D Rowland, K Smyth, and R Friedland. "Smoking and oestrogen-replacement therapy as protective factors for Alzheimer's disease." *Lancet* 349.9049 (1997): 403-4.
110. Plassman, BL, MJ Helms, KA Welsh, AM Saunders, and JC. Breitner. "Smoking, Alzheimer's disease, and confounding with genes." *Lancet* 345.8946 (1995): 387.

-
111. Prince, M, M Cullen, and A Mann. "Risk factors for Alzheimer's disease and dementia: a case-control study based on the MRC Elderly Hypertension Trial." *Neurology* 44.1 (1994): 97-104.
112. Salib, E, and V Hillier. "A case-control study of smoking and Alzheimer's disease." *International Journal of Geriatric Psychiatry* 12.3 (1997): 295-300.
113. Shaji, S, K Promodu, T Abraham, KJ Roy, A Verghese. "An epidemiological study of dementia in a rural community in Kerala, India." *British Journal of Psychiatry* 168.6 (1996): 745-9.
114. Canadian Study of Health and Aging. "Risk factors for Alzheimer's disease in Canada." *Neurology* 44 (1994): 2073-80.
115. van Duijn, CM, and A Hofman. "Relation between nicotine intake and Alzheimer's disease." *British Medical Journal* 302.6791 (1991): 1491-4.
116. Wang, PN, SJ Wang, CJ Hong, TT Liu, JL Fuh, CW Chi, CY Liu, and HC Liu. "Risk factors for Alzheimer's disease: a case-control study." *Neuroepidemiology* 16.5 (1997): 234-40.
117. Wang, HX, L Fratiglioni, GB Frisoni, M Viitanen, and B Winblad. "Smoking and the occurrence of Alzheimer's disease: cross-sectional and longitudinal data in a population-based study." *American Journal of Epidemiology* 149.7 (1999): 640-4.
118. Doll, R, R Peto, J Boreham, and I Sutherland. "Smoking and dementia in male British doctors: prospective study." *British Medical Journal* 320.7242 (2000): 1097-1102.
119. Hebert, LE, PA Scherr, LA Beckett, HH Funkenstein, MS Albert, MJ Chown, and DA Evans. "Relation of smoking and alcohol consumption to incident Alzheimer's disease." *American Journal of Epidemiology* 135.4 (1992): 347-55.
120. Hirayama, T. "Large cohort study on the relation between cigarette smoking and senile dementia without cerebrovascular lesions." *Tobacco Control* 1.3 (1992): 176-9.
121. Katzman, R, M Aronson, P Fuld, C Kawas, T Brown, H Morgenstern, W Frishman, L Gidez, H Eder, and WL Ooi. "Development of dementing illnesses in an 80-year-old volunteer cohort." *Annals of Neurology* 25.4 (1989): 317-24.
122. Launer, LJ, K Andersen, ME Dewey, L Letenneur, A Ott, LA Amaducci, C Brayne, JR Copeland, JF Dartigues, P Kragh-Sorensen, A Lobo, JM Martinez-Lage, T Stijnen, and A Hofman. "Rates and risk

-
- factors for dementia and Alzheimer's disease: results from EURODEM pooled analysis." *Neurology* 52.1 (1999): 78–84.
123. Merchant, C, MX Tang, S Albert, J Manly, Y Stern, and R Mayeux. "The influence of smoking on the risk of Alzheimer's disease." *Neurology* 52.7 (1999): 1408–12.
124. Ott, A, AJ Slioter, A Hofman, F van Harskamp, JC Witteman, C Van Broeckhoven, CM van Duijn, and MM Breteler. "Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study." *Lancet* 351.9119 (1998): 1840–3.
125. Broe, GA, H Creasey, AF Jorm, HP Bennett, B Casey, LM Waite, DA Grayson, and J Cullen. "Health habits and risk of cognitive impairment and dementia in old age: a prospective study on the effects of exercise, smoking and alcohol consumption." *Australian and New Zealand Journal of Public Health* 22.5 (1998): 621–3.
126. Juan, D, DH Zhou, J Li, JY Wang, C Gao, and Chen M.. "A 2-year follow-up study of cigarette smoking and risk of dementia." *European Journal of Neurology* 11.4 (2004): 277–82.
127. Laurin, D, KH Masaki, DJ Foley, LR White, and LJ Launer. "Midlife dietary intake of antioxidants and risk of late-life incident dementia: the Honolulu-Asia Aging Study." *American Journal of Epidemiology* 159.10 (2004): 959–67.
128. Moffat, SD, AB Zonderman, EJ Metter, C Kawas, MR Blackman, SM Harman, and SM Resnick. "Free testosterone and risk for Alzheimer disease in older men." *Neurology* 62.2 (2004): 188–93.
129. Luchsinger, JA, C Reitz, LS Honig, MX Tang, S Shea, and R Mayeux.. "Aggregation of vascular risk factors and risk of incident Alzheimer disease." *Neurology* 65.4 (2005): 545–51.
130. Tyas, SL, LR White, H Petrovitch, G Webster Ross, DJ Foley, HK Heimovitz, and LJ Launer. "Mid-life smoking and late-life dementia: the Honolulu-Asia Aging Study." *Neurobiology of Aging* 24.4 (2003): 589–96.
131. Aggarwal, N, JL Bienias, DA Bennett, RS Wilson, MC Morris, JA Schneider, RC Shah, and DA Evans. "The relation of cigarette smoking to incident Alzheimer's disease in a biracial urban community population." *Neuroepidemiology* 26.3 (2006): 140–6.

-
132. Reitz, C, T den Heijer, C van Duijn, A Hofman, and MM Breteler. "Relation between smoking and risk of dementia and Alzheimer disease: the Rotterdam Study." *Neurology* 69.10 (2007): 998-1005.
133. Kivipelto, M, S Rovio, T Ngandu, I Kåreholt, M Eskelinen, B Winblad, V Hachinski, A Cedazo-Minguez, H Soininen, J Tuomilehto, and A Nissinen. "Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study." *Journal of Cellular and Molecular Medicine* 12.6B (2008): 2762–71.
134. Egan, M, A Maclean, H Sweeting, and K Hunt. "Comparing the effectiveness of using generic and specific search terms in electronic databases to identify health outcomes for a systematic review: a prospective comparative study of literature search methods." *British Medical Journal* 2.3 (2012).
135. Szklo, M, and FJ Nieto. *Epidemiology: Beyond the Basics*. (Sudbury, Mass. Toronto: Jones and Bartlett Publishers, 2007) 174.
136. Siontis, KC, T Hernandez-Boussard, JP Ioannidis. "Overlapping meta-analyses on the same topic: survey of published studies." *British Medical Journal* 347 (2013): f4501.
137. Merrill, RM. *Introduction to Epidemiology*. (Sudbury, Mass: Jones and Bartlett Publishers, 2010) 171.
138. Riggs, JE. "Smoking and Alzheimer's disease: protective effect or differential survival bias?" *The Lancet* 342.8874 (1993): 793-4.
139. Stuber, J, S Galea, and BG Link. "Smoking and the emergence of a stigmatized social status." *Social Science and Medicine* 67.3 (2008): 420-30.
140. Hald, J, J Overgaard, C Grau. "Evaluation of objective measures of smoking status: a prospective clinical study in a group of head and neck cancer patients treated with radiotherapy." *Acta Oncologica* 42.2 (2003): 154-9.
141. Fotuhi, M, P Mohassel, and K Yaffe. "Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: a complex association." *Nature Clinical Practice* 5.3 (2009): 140 – 152.
142. Issa, AM, WA Mojica, SC Morton, S Traina, SJ Newberry, LG Hilton, RH Garland, and CH Maclean. "The efficacy of omega-3 fatty acids on cognitive function in aging and dementia: a systematic review." *Dementia & Geriatric Cognitive Disorders* 21.2 (2006): 88-96.
143. Lim, WS, JK Gammack, J Van Niekerk, and AD Dangour. "Omega 3 fatty acid for the prevention of dementia." *Cochrane Database of Systematic Reviews* 1 (2006): CD005379.

-
144. Dangour, AD, PJ Whitehouse, K Rafferty, SA Mitchell, L Smith, S Hawkesworth, and B Vellas. "B-Vitamins and Fatty Acids in the Prevention and Treatment of Alzheimer's Disease and Dementia: A Systematic Review." *Journal of Alzheimer's Disease* 22.1 (2010): 205-224.
145. Barberger-Gateau, P, L Letenneur, V Deschamps, K Pérès, JF Dartigues, and S Renaud. "Fish, meat, and risk of dementia: cohort study." *British Medical Journal* 325.7370 (2002): 932-933.
146. Kalmijn, S, LJ Launer, A Ott, JC Witteman, A Hofman, and MM Breteler. "Dietary fat intake and the risk of incident dementia in the Rotterdam study." *Annals of Neurology* 42.5 (1997): 776-782.
147. Morris, MC, DA Evans, JL Bienias, CC Tangney, DA Bennett, RS Wilson, N Aggarwal, and J Schneider. "Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease." *Archives of Neurology* 60.7 (2003): 940-946.
148. Engelhart, MJ, MI Geerlings, A Ruitenberg, JC Van Swieten, A Hofman, JC Witteman, and MM Breteler. "Diet and risk of dementia: Does fat matter? The Rotterdam Study." *Neurology* 59.12 (2002): 1915-1921.
149. Huang, TL, PP Zandi, KL Tucker, AL Fitzpatrick, LH Kuller, LP Fried, GL Burke, and MC Carlson. "Benefits of fatty fish on dementia risk are stronger for those without APOE epsilon4." *Neurology* 65.9 (2005): 1409-1414.
150. Schaefer, EJ, V Bongard, AS Beiser, S Lamon-Fava, SJ Robins, R Au, KL Tucker, DJ Kyle, PW Wilson, and PA Wolf. "Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study." *Archives of Neurology* 63.11 (2006): 1545-1550.
151. Laitinen, MH, T Ngandu, S Rovio, EL Helkala, U Uusitalo, M Viitanen, A Nissinen, J Tuomilehto, H Soininen, and M Kivipelto. "Fat intake at midlife and risk of dementia and Alzheimer's disease: a population-based study." *Dementia and Geriatric Cognitive Disorders* 22.1 (2006): 99-107.
152. Barberger-Gateau, P, C Raffaitin, L Letenneur, C Berr, C Tzourio, JF Dartigues, and A Alperovitch. "Dietary patterns and risk of dementia: the Three-City cohort study." *Neurology* 69.20 (2007): 1921-30.
153. Samieri, C, C Féart, L Letenneur, JF Dartigues, K Pérès, S Auriacombe, E Peuchant, C Delcourt, and P Barberger-Gateau. "Low plasma eicosapentaenoic acid and depressive symptomatology are independent predictors of dementia risk." *American Journal of Clinical Nutrition* 88.3 (2008): 714-21.

-
154. Laurin, D, R Verreault, J Lindsay, E Dewailly, and BJ Holub. "Omega-3 fatty acids and risk of cognitive impairment and dementia." *Journal of Alzheimers Disease* 5.4 (2003): 315-22.
155. Kroger, E, R Verreault, PH Carmichael, J Lindsay, P Julien, E Dewailly, P Ayotte, and D Laurin. "Omega-3 fatty acids and risk of dementia: the Canadian Study of Health and Aging." *American Journal of Clinical Nutrition* 90.1 (2009): 184-92.
156. Devore, EE, F Grodstein, FJ van Rooij, A Hofman, B Rosner, MJ Stampfer, JC Witteman, and MM Breteler. "Dietary intake of fish and omega-3 fatty acids in relation to long-term dementia risk." *American Journal of Clinical Nutrition* 90.1 (2009): 170-6.
157. Kristal, AR, U Peters, and JD Potter. "Is It Time to Abandon the Food Frequency Questionnaire?" *Cancer Epidemiology, Biomarkers & Prevention* 14.12 (2005): 2826.
158. McCaddon, A. "Homocysteine and cognitive impairment; a case series in a General Practice setting." *Nutrition Journal* 5 (2006).
159. Morris, MC, JA Schneider, and CC Tangney. "Thoughts on B-vitamins and dementia." *Journal of Alzheimer's Disease* 9.4 (2006): 429-33.
160. Mizrahi, EH, A Bowirrat, DW Jacobsen, AD Korczyn, F Traore, GJ Petot, AJ Lerner, SM Debanne, A Adunsky, PM Dibello, and RP Friedland. "Plasma homocysteine, vitamin B12 and folate in Alzheimer's patients and healthy Arabs in Israel." *Journal of the Neurological Sciences* 227.1 (2004): 109-13.
161. Maxwell, CJ, DB Hogan, and EM Ebly. "Serum folate levels and subsequent adverse cerebrovascular outcomes in elderly persons." *Dementia and Geriatric Cognitive Disorders* 13.4 (2002): 225-34.
162. Quadri, P, C Fragiaco, R Pezzati, E Zanda, G Forloni, M Tettamanti, and U Lucca. "Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia." *American Journal of Clinical Nutrition* 80.1 (2004): 114-22.
163. Bowirrat, A, RP Friedland, L Farrer, C Baldwin, and A Korczyn. "Genetic and environmental risk factors for Alzheimer's disease in Israeli Arabs." *Journal of Molecular Neuroscience* 19.1-2 (2002): 239-45.
164. Anello, G, RM Guéant-Rodríguez, P Bosco, JL Guéant, A Romano, B Namour, R Spada, F Caraci, G Pourié, JL Daval, and R Ferri. "Homocysteine and methylenetetrahydrofolate reductase polymorphism in Alzheimer's disease." *Neuroreport* 15.5 (2004): 859-61.

-
165. Mizrahi, EH, DW Jacobsen, SM Debanne, F Traore, AJ Lerner, RP Friedland, and GJ Petot. "Plasma total homocysteine levels, dietary vitamin B6 and folate intake in AD and healthy aging." *Journal of Nutrition, Health and Aging* 7.3 (2003): 160-5.
166. Douaud, G, H Refsum, CA de Jager, R Jacoby, TE Nichols, SM Smith, and AD Smith. "Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment." *Proceedings of the National Academy of Sciences of the United States of America* 110.23 (2013).
167. Dierkes, J, C Luley, and S Westphal. "Effect of lipid-lowering and antihypertensive drugs on plasma homocysteine levels." *Vascular Health and Risk Management* 3.1 (2007): 99-108.
168. Letenneur, L, C Proust-Lima, A Le Gouge, JF Dartigues, and P Barberger-Gateau. "Flavonoid intake and cognitive decline over a 10-year period." *American Journal of Epidemiology* 165.12 (2007): 1364-71.
169. Raman, G, A Tatsioni, M Chung, IH Rosenberg, J Lau, AH Lichtenstein, and EM Balk. "Heterogeneity and lack of good quality studies limit association between folate, vitamins B-6 and B-12, and cognitive function." *Journal of Nutrition* 137.7 (2007): 1789-94.
170. Pham, DQ, and R Plakogiannis. "Vitamin E Supplementation in Alzheimer's Disease, Parkinson's Disease, Tardive Dyskinesia, and Cataract: Part 2." *Annals of Pharmacotherapy* 39.12 (2005): 2065-72.
171. Clarke, R, AD Smith, KA Jobst, H Refsum, L Sutton, and PM Ueland. "Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease." *Archives of Neurology* 55.11 (1998): 1449-1455.
172. Ravaglia, G, P Forti, F Maioli, M Martelli, L Servadei, N Brunetti, E Porcellini, and F Licastro. "Homocysteine and folate as risk factors for dementia and Alzheimer disease." *American Journal of Clinical Nutrition* 82.3 (2005): 636-643.
173. Seshadri, S, A Beiser, J Selhub, PF Jacques, IH Rosenberg, RB D'Agostino, PW Wilson, and PA Wolf. "Plasma homocysteine as a risk factor for dementia and Alzheimer's disease." *New England Journal of Medicine* 346.7 (2002): 476-483.
174. Wang, HX, A Wahlin, H Basun, J Fastbom, B Winblad, and L Fratiglioni. "Vitamin B (12) and folate in relation to the development of Alzheimer's disease." *Neurology* 56.9 (2001): 1188-1194.

-
175. Morris, MC, DA Evans, JA Schneider, CC Tangney, JL Bienias, and NT Aggarwal. "Dietary folate and vitamins B12 and B6 not associated with incident Alzheimer's disease." *Journal of Alzheimer's Disease* 9.4 (2006): 435-443.
176. Annerbo, S, LO Wahlund, and J Lökk. "The significance of thyroid stimulating hormone and homocysteine in the development of Alzheimer's disease in mild cognitive impairment: a 6 year follow up study." *American Journal of Alzheimer's disease and Other Dementias* 21.3 (2006): 182-8.
177. Corrada, MM, CH Kawas, J Hallfrisch, D Muller and R Brookmeyer. "Reduced risk of Alzheimer's disease with high folate intake: The Baltimore Longitudinal Study of Aging." *Alzheimer's and Dementia* 1.1 (2005): 1118.
178. Luchsinger, JA, MX Tang, J Miller, R Green, and R Mayeux. "Relation of higher folate intake to lower risk of Alzheimer disease in the elderly." *Archives of Neurology* 64.1 (2007): 8692.
179. Miller, JW, R Green, DM Mungas, BR Reed, and WJ Jagust. "Homocysteine, vitamin B6, and vascular disease in AD patients." *Neurology* 58.10 (2002): 1471-5.
180. Morris, MC, DA Evans, JL Bienias, PA Scherr, CC Tangney, LE Hebert, DZ Bennett, RS Wilson, and N Aggarwal. "Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline." *Journal of Neurology, Neurosurgery, and Psychiatry* 75.8 (2004): 1093-99.
181. Engelhart, MJ, MI Geerlings, A Ruitenberg, JC van Swieten, A Hofman, JC Witteman, and MM Breteler. "Dietary intake of antioxidants and risk of Alzheimer's disease." *Journal of the American Medical Association* 287.24 (2002): 3223-9.
182. Morris, MC, DA Evans, JL Bienias, CC Tangney, DA Bennett, N Aggarwal, RS Wilson, and PA Scherr. "Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study." *Journal of the American Medical Association* 287.24 (2002): 3230-7.
183. Masaki, KH, KG Losonczy, G Izmirlian, DJ Foley, GW Ross, H Petrovitch, R Havlik, and LR White. "Association of vitamin E and C supplement use with cognitive function and dementia in elderly men." *Neurology* 54.6 (2000): 1265-72.

-
184. Helmer, C, E Peuchant, L Letenneur, I Bourdel-Marchasson, S Larrieu, JF Dartigues, L Dubourg, MJ Thomas, and P Barberger-Gateau. "Association between antioxidant nutritional indicators and the incidence of dementia: results from the PAQUID prospective cohort study." *European Journal of Clinical Nutrition* 57.12 (2003): 1555–61.
185. Dai, Q, AR Borenstein, Y Wu, JC Jackson, and EB Larson. "Fruit and vegetable juices and Alzheimer's disease: the Kame Project." *American Journal of Medicine* 119.9 (2006): 751–9.
186. Laurin, D, KH Masaki, DJ Foley, LR White, and LJ Launer. "Midlife dietary intake of antioxidants and risk of late-life incident dementia: the Honolulu-Asia Aging Study." *American Journal of Epidemiology* 159.10 (2004): 959–67.
187. Luchsinger, JA, MX Tang, S Shea, and R Mayeux. "Antioxidant vitamin intake and risk of Alzheimer disease." *Archives of Neurology* 60.2 (2003): 203–8.
188. Fillenbaum, GG, et al. "Dementia and Alzheimer's disease in community-dwelling elders taking vitamin C and/or vitamin E." *Annals of Pharmacotherapy* 39.12 (2005):2009-14.
189. Gray, SL, ML Anderson, PK Crane, JC Breitner, W McCormick, JD bowen, L Teri, and E Larson. "Antioxidant vitamin supplement use and risk of dementia or Alzheimer's disease in older adults." *Journal of the American Geriatric Society* 56.2 (2008):291-5.
190. Maxwell, CJ, MS Hicks, DB Hogan, J Basran, and EM Ebly. "Supplemental use of antioxidant vitamins and subsequent risk of cognitive decline and dementia." *Dementia and Geriatric Cognitive Disorders* 20.1 (2005): 45-51.
191. Morris, MC, LA Beckett, PA Scherr, LE Hebert, DA Bennett, TS Field, and DA Evans. "Vitamin E and vitamin C supplement use and risk of incident Alzheimer disease." *Alzheimer Disease and Associated Disorders* 12.3 (1998): 121-6.
192. Zandi, PP, JC Anthony, AS Khachaturian, SV Stone, D Gustafson, JT Tschanz, MC Norton, KA Welsh-Bohmer, and JC Breitner. "Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study." *Archives of Neurology* 61.1 (2004):82-8.

-
193. Morris, MC, DA Evans, CC Tangney, JL Bienias, RS Wilson, NT Aggarwal, PA Scherr. "Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change." *American Journal of Clinical Nutrition* 81.2 (2005): 508-14.
194. Commenges, D, V Scotet, S Renaud, H Jacqmin-Gadda, P Barberger-Gateau, and JF Dartigues.. "Intake of flavonoids and risk of dementia." *European Journal of Epidemiology* 16.4 (2000): 357-63.
195. Jacobs, DR, LC Tapsell, and NJ Temple. "Food synergy: the key to balancing the nutrition research effort." *Public Health Reviews* 33.2 (2011): 507-29.
196. Hughes, TF, R Andel, BJ Small, AR Borenstein, JA Mortimer, A Wolk, B Johansson, L Fratiglioni, NL Pedersen, and M Gatz. "Midlife fruit and vegetable consumption and risk of dementia in later life in Swedish twins." *American Journal of Geriatric Psychiatry* 18.5 (2010).
197. Santos, C, J Costa, J Santos, A Vaz-Carneiro, and N Lunet. "Caffeine intake and dementia: systematic review and meta-analysis." *Journal of Alzheimer's Disease* 20 Suppl 1.(2010): S187-204.
198. Barranco Quintana, JL, MF Allam, A Serrano Del Castillo, and R Fernández-Crehuet Navajas. "Alzheimer's disease and coffee: a quantitative review." *Neurological Research* 29.1 (2007): 91-5.
199. Eskelinen, MH, and M Kivipelto. "Caffeine as a Protective Factor in Dementia and Alzheimer's Disease." *Journal of Alzheimer's Disease* 20. Suppl 1 (2010): S167-S174.
200. Maia, L, and A de Mendonca. "Does caffeine intake protect from Alzheimer's disease?" *European Journal of Neurology* 9.4 (2002): 377-382.
201. Tyas, SL, J Manfreda, LA Strain, and PR Montgomery. "Risk factors for Alzheimer's disease: A population based longitudinal study in Manitoba, Canada." *International Journal of Epidemiology* 30.3 (2001): 590-597.
202. Eskelinen, MH, T Ngandu, J Tuomilehto, H Soininen, and M Kivipelto. "Midlife coffee and tea drinking and the risk of late-life dementia: a population-based CAIDE study." *Journal of Alzheimer's Disease* 16.1 (2009): 85-91.
203. Cross, AJ, JM Major, and R Sinha. "Urinary Biomarkers of Meat Consumption." *Cancer Epidemiology, Biomarkers & Prevention* 20. (2011): 1107.

-
204. Chan, Q, J Stamler, J Posma, I Garcia, A Wijeyesekera, LO Griep, L Van Horn, ML Daviglus, K Miura, L Zhao, JK Nicholson, E Holmes, P Elliot, and the INTERMAP Rsch group. "Relationship of coffee consumption and its urinary biomarker to blood pressure: the Intermap Study." *Circulation* 127.AP267 (2013).
205. Scarmeas, N, Y Stern, R Mayeux, and JA Luchsinger. "Mediterranean Diet, Alzheimer Disease, and Vascular Mediation." *Archives of Neurology* 63.12 (2006): 1709-17.
206. Roman, B, L Carta, MA Martínez-González, and L Serra-Majem. "Effectiveness of the Mediterranean diet in the elderly." *Clinical Interventions in Aging* 3.1 (2008): 97-109.
207. Scarmeas, N, Y Stern, MX Tang, R Mayeux, and JA Luchsinger. "Mediterranean diet and risk for Alzheimer's disease." *Annals of Neurology* 59.6 (2006): 912-921.
208. Sofi, F, F Cesari, R Abbate, GF Gensini, and A Casini. "Adherence to Mediterranean diet and health status: meta-analysis." *British Medical Journal* 337 (2008): a1344.
209. Sofi, F, R Abbate, GF Gensini, and A Casini. "Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis." *American Journal of Clinical Nutrition* 92.5 (2010): 1189-96.
210. Feart, C, C Samieri, V Rondeau, H Amieva, F Portet, JF Dartigues, N Scarmeas, and P Barberger-Gateau. "Adherence to a Mediterranean diet, cognitive decline, and risk of dementia." *Journal of the American Medical Association* 302.6 (2009): 638-48.
211. Scarmeas, N, JA Luchsinger, N Schupf, AM Brickman, S Cosentino, MX Tang, and Y Stern. "Physical activity, diet, and risk of Alzheimer disease." *Journal of the American Medical Association* 302.6 (2009): 627-37.
212. Scarmeas, N, Y Stern, R Mayeux, JJ Manly, N Schupf, and JA Luchsinger.. "Mediterranean diet and mild cognitive impairment." *Archives of Neurology* 66.2 (2009): 216-25.
213. Morris, MC. "The role of nutrition in Alzheimer's disease: epidemiological evidence." *European Journal of Neurology* 16.Suppl 1 (2009): 1-7.

-
214. Crichton, GE, J Bryan, KJ Murphy, and J Buckley. "Review of dairy consumption and cognitive performance in adults: findings and methodological issues." *Dementia & Geriatric Cognitive Disorders* 30.4 (2010): 352-61.
215. Luchsinger, JA, MX Tang, S Shea, and R Mayeux. "Caloric intake and the risk of Alzheimer disease." *Archives of Neurology* 59.8 (2002): 1258-63.
216. Morris, MC, DA Evans, JL Bienias, CC Tangney, DA Bennett, N Aggarwal, J Schneider, and RS Wilson. "Dietary fats and the risk of incident Alzheimer disease." *Archives of Neurology* 60.2 (2003): 194-200.
217. Laitinen, MH, T Ngandu, S Rovio, EL Helkala, U Uusitalo, M Viitanen, A Nissinen, J Tuomilehto, H Soininen, and M Kivipelto. "Fat intake at midlife and risk of dementia and Alzheimer's disease: a population-based study." *Dementia and Geriatric Cognitive Disorders* 22.1 (2006): 99-107.
218. Lichtenstein, AH. "Dietary fat and cardiovascular disease risk: quantity or quality?" *Journal of Women's Health* 12.2 (2003): 109-14.
219. Sharp, ES, and M Gatz. "The relationship between education and dementia an updated systematic review." *Alzheimer Disease and Associated Disorders* 25.4 (2011): 289-304.
220. McDowell, I, G Xi, J Lindsay, and M Tierney. "Mapping the connections between education and dementia." *Journal of Clinical and Experimental Neuropsychology* 29.2 (2007): 127-141.
221. Stern, Y. "Cognitive reserve and Alzheimer disease." *Alzheimer Disease and Associated Disorders* 20 (2006): S69-74.
222. Vance, DE, and M Crowe. "A proposed model of neuroplasticity and cognitive reserve in older adults." *Activities, Adaptation and Aging* 30.3 (2006): 61-79.
223. Vance, DE, J Kaur, PL Fazeli, MH Talley, HK Yuen, B Kitchin, and F Lin. "Neuroplasticity and successful cognitive aging: a brief overview for nursing." *Journal of Neuroscience Nursing* 44.4 (2012).
224. Fjell, AM, KB Walhovd, I Reinvang, A Lundervold, D Salat, BT Quinn, B Fischl, and AM Dale. "Selective increase of cortical thickness in high-performing elderly – structural indices of optimal cognitive aging." *NeuroImage* 29.3 (2006): 984-994.

-
225. Anstey, KJ, "Optimizing cognitive development over the life course and preventing cognitive decline: introducing the Cognitive Health Environment Life Course Model (CHELM)." *International Journal of Behavioral Development* 38.1 (2014): 1-10.
226. Geerlings, MA, DJ Deeg, BW Penninx, B Schmand, C Jonker, LM Bouter, and W van Tilburg. "Cognitive reserve and mortality in dementia: the role of cognition, functional ability and depression." *Psychological Medicine* 29.5 (1999): 1219-1226.
227. London, M. *The Oxford Handbook of Lifelong Learning*. (Oxford: Oxford University Press, USA, 2011)
Internet resource.
228. Prakash, J, V Ryali, K Srivastava, PS Bhat, and R Shashikumar. "Cognitive reserve: the warehouse within." *Industrial Psychiatry Journal* 20.2 (2011): 79-82.
229. Iqbal, K, SS Sisodia, and B Winblad. *Alzheimer's Disease: Advances in Etiology, Pathogenesis and Therapeutics*. (Chichester: John Wiley & Sons, 2001). Internet resource.
230. Stamler, J, P Elliot, L Appel, Q Chan, M Buzzard, B Dennis, AR Dyer, P Elmer, P Greenland, D Jones, H Kesteloot, L Kuller, D Labarthe, K Liu, A Moag-Stahlberg, M Nichaman, A Okayama, N Okuda, C Robertson, B Rodriguez, M Stevens, H Ueshima, L Van Horn, and B Zhou. "Higher blood pressure in middle-aged American adults with less education – role of multiple dietary factors: the INTERMAP Study." *Journal of Human Hypertension* 17 (2003): 655-64.
231. Caamano-Isorna, F, M Corral, A Montes-Martínez, and B Takkouche. "Education and Dementia : A Meta-Analytic Study." *Neuroepidemiology* 26.4 (2006): 226-232.
232. Cobb, JL, PA Wolf, R Au, R White, and RB D'Agostino. "The effect of education and the incidence of dementia and Alzheimer's disease in the Framingham Study." *Neurology* 45.9 (1995): 1707-12.
233. Ott, A, CT van Rossum, F van Harskamp, H van de Mheen, A Hofman, and MM Breteler. "Education and the incidence of dementia in a large population-based study: the Rotterdam Study." *Neurology* 52.3 (1999): 663-6.

-
234. Letenneur, L, V Gilleron, D Commenges, C Helmer, JM Orgogozo, and JF Dartigues. "Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project." *Journal of Neurology, Neurosurgery, and Psychiatry* 66.2 (1999): 177-183.
235. Scarmeas, N, G Levy, MX Tang, J Manly, and Y Stern. "Influence of leisure activity on the incidence of Alzheimer's disease." *Neurology* 57.12 (2001): 2236-42.
236. Kukull, WA, R Higdon, JD Bowen, WC McCormick, L Teri, GD Schellenberg, G van Belle, L Jolley, and EB Larson. "Dementia and Alzheimer disease incidence: a prospective cohort study." *Archives of Neurology* 59.11 (2002): 1737-46.
237. Di Carlo, A, M Baldereschi, L Amaducci, V Lepore, L Bracco, S Maggi, S Bonaiuto, E Perissinotto, G Scarlato, G Farchi, and D Inzitari. "Incidence of dementia, Alzheimer's disease, and vascular dementia in Italy: The ILSA Study." *Journal of the American Geriatric Society* 50.1 (2002): 41-8.
238. Karp, A, I Kåreholt, C Qiu, T Bellander, B Winblad, and L Fratiglioni. "Relation of education and occupation-based socioeconomic status to incident Alzheimer's disease." *American Journal of Epidemiology* 159.2 (2004): 175-83.
239. Beard, CM, E Kokmen, KP Offord, and LT Kurland. "Lack of association between Alzheimer's disease and education, occupation, marital status, or living arrangement." *Neurology* 42.11 (1992): 2063-8.
240. Gatz, M, P Svedberg, NL Pedersen, JA Mortimer, S Berg, and B Johansson. "Education and the risk of Alzheimer's disease: findings from the study of dementia in Swedish twins." *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* 56.5 (2001): 292-300.
241. Harmanci, H, M Emre, H Gurvit, B Bilgic, H Hanagasi, E Gurol, H Sahin, and S Tinaz. "Risk factors for Alzheimer disease: a population-based case-control study in Istanbul, Turkey." *Alzheimer's Disease and Associated Disorders* 17.3 (2003): 139-45.
242. Ngandu, T, E von Strauss, EL Helkala, B Winblad, A Nissinen, J Tuomilehto, H Soininen, and M Kivipelto. "Education and dementia: what lies behind the association?" *Neurology* 69.14 (2007): 1442-50.
243. Tyas, SL, JC Salazar, DA Snowdon, MF Desrosiers, KP Riley, MS Mendiondo, and RJ Kryscio. "Transitions to mild cognitive impairments, dementia, and death: findings from the Nun Study." *American Journal of Epidemiology* 165.11 (2007): 1231-8.

-
244. Steffener, J, and Y Stern. "Exploring the neural basis of cognitive reserve in aging." *Biochimica et Biophysica Acta* 1822.3 (2012): 467-73.
245. Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 268.
246. Meng, X, and C D'Arcy. "Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses." *PLoS ONE* [Electronic Resource] 7.6 (2012): e38268.
247. Scarmeas, N, and Y Stern. "Cognitive reserve and lifestyle." *Journal of clinical and experimental neuropsychology* 25.5 (2003): 625-33.
248. Shi, L, and DA Singh. *The Nation's Health*. (Sudbury, MA: Jones & Bartlett Learning, 2011). Print.
249. Chapman, S, S Aslan, JS Spence, JJ Hart Jr, EK Bartz, N Didehbani, MW Keebler, CM Gardner, JF Strain, LF Defina, and H Lu. "Neural mechanisms of brain plasticity with complex cognitive training in healthy seniors." *Cerebral Cortex* (2013).
250. Stern, Y. "Cognitive Reserve." *Neuropsychologia* 47.10 (2009): 2015-28.
251. Fratiglioni, L, S Paillard-Borg, and B Winblad. "An active and socially integrated lifestyle in late life might protect against dementia." *Lancet Neurology* 3.6 (2004): 343-53.
252. Fabrigoule, C, L Letenneur, JF Dartigues, M Zarrouk, D Commenges, and P Barberger-Gateau. "Social and leisure activities and risk of dementia: a prospective longitudinal study." *Journal of the American Geriatric Society* 43.5 (1995): 485-90.
253. Scarmeas, N, G Levy, MX Tang, J Manly, and Y Stern. "Influence of leisure activity on the incidence of Alzheimer's disease." *Neurology* 57.12 (2001): 2236-42.
254. Wilson, RS, DA Bennett, JL Bienias, NT Aggarwal, CF Mendes De Leon, MC Morris, JA Schneider, and DA Evans. "Cognitive activity and incident AD in a population-based sample of older persons." *Neurology* 59.12 (2002): 1910-4.

-
255. Wilson, RS, CF Mendes De Leon, LL Barnes, JA Schneider, JL Bienias, DA Evans, and DA Bennett. "Participation in cognitively stimulating activities and risk of incident Alzheimer disease." *Journal of the American Medical Association* 287.6 (2002): 742–8.
256. Verghese, J, RB Lipton, MJ Katz, CB Hall, CA Derby, G Kuslansky, AF Ambrose, M Sliwinski, and H Buschke. "Leisure activities and the risk of dementia in the elderly." *New England Journal of Medicine* 348 (2003): 2508–16.
257. Friedland, RP, T Fritsch, KA Smyth, E Koss, AJ Lerner, CH Chen, GJ Petot, and SM Debanne. "Patients with Alzheimer's Disease have reduced activities in midlife compared with healthy control-group members." *Proceedings of the National Academy of Sciences* 98.6 (2001): 3440–5.
258. Fritsch, T, KA Smyth, SM Debanne, GJ Petot, and RP Friedland. "Participation in novelty-seeking leisure activities and Alzheimer's Disease." *Journal of Geriatric Psychiatry and Neurology* 18.3 (2005): 134–41.
259. Crowe, M, R Andel, NL Pedersen, B Johansson, and M Gatz. "Does participation in leisure activities lead to reduced risk of Alzheimer's Disease? A prospective study of Swedish twins." *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* 58.5 (2003): P249-55.
260. Lindstrom, HA, T Fritsch, G Petot, KA Smyth, CH Chen, SM Debanne, AJ Lerner, and RP Friedland. "The relationships between television viewing in midlife and the development of Alzheimer's Disease in a case–control study." *Brain and Cognition* 58.2 (2005): 157-65.
261. Kondo, K, M Niino, and K Shido. "A case-control study of Alzheimer's disease in Japan: significance of life-styles." *Dementia* 5.6 (1994): 314-26.
262. He, YL, XK Zhang, and MY Zhang. "Psychosocial risk factors for Alzheimer's disease." *Hong Kong Journal of Psychiatry* 10.2 (2000): 2-7.
263. Wilson, RS, PA Scherr, JA Schneider, Y Tang, and DA Bennett. "Relation of cognitive activity to risk of developing Alzheimer disease." *Neurology* 69.20 (2007): 1911–20.
264. Akbaraly, TN, F Portet, S Fustini, JF Dartigues, S Artero, O Rouaud, J Touchon, K Ritchie, and C Berr. "Leisure activities and the risk of dementia in the elderly: results from the Three-City Study." *Neurology* 73.11 (2009): 854-61.

-
265. La Rue, A. *Healthy brain aging: Role of cognitive reserve, cognitive stimulation and cognitive exercises*, In A. K. Desai (Ed.). *The healthy aging brain: Evidence based methods to preserve brain function and prevent dementia*, Clinics in Geriatric Medicine, 26 (2010): 99–111.
266. Hamer, M, and Y Chida, “Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence.” *Psychological Medicine* 39.1 (2009): 3-11.
267. Stern, C, and R Konno. “Physical leisure activities and their role in preventing dementia: a systematic review.” *International Journal of Evidence Based Healthcare* 7.4 (2009): 270-82.
268. Erickson, KI, AM Weinstein, and OL Lopez. “Physical activity, brain plasticity, and Alzheimer’s disease.” *Archives of Medical Research* 43.8 (2012): 615-21.
269. Kramer, AF, H Sowon, and E McAuley. “Influence of aerobic fitness on the neurocognitive function of older adults.” *Journal of Aging and Physical Activity* 8.4 (2000): 379-85.
270. Podewils, LJ. “Physical activity and dementia risk: a systematic review.” Dissertation, Johns Hopkins University, 2003, Web.
271. Penrose, FK. “Can exercise affect cognitive functioning in Alzheimer’s disease? A review of the literature.” *Activities, Adaptation & Aging* 29.4 (2005): 15-40.
272. Rolland, Y, G Abellan van Kan, and B Vellas. “Physical activity and Alzheimer’s disease: from prevention to therapeutic perspectives.” *Journal of the American Medical Directors Association* 9.6 (2008): 390-405.
273. Weih, M, Ü Degirmenci, S Kreil, and J Kornhuber. “Physical activity and Alzheimer’s disease: a meta-analysis of cohort studies.” *GeroPsych* 23.1 (2010): 17-20.
274. Hurley, BF, ED Hanson, and AK Sheaff. “Strength Training as a Countermeasure to Aging Muscle and Chronic Disease.” *Sports Medicine* 41.4 (2011): 289-306.
275. Helmer, C, D Damon, L Letenneur, C Fabrigoule, P Barberger-Gateau, S Lafont, R Fuhrer, T Antonucci, D Commenges, JM Orgogozo, and JF Dartigues. “Marital status and risk of Alzheimer’s disease: a French population-based cohort study.” *Neurology* 53.9 (1999): 1953-8.
276. Scarmeas, N, G Levy, MX Tang, J Manly, and Y Stern. “Influence of leisure activity on the incidence of Alzheimer’s disease.” *Neurology* 57.12 (2001): 2236-42.

-
277. Wang, HX, A Karp, B Winblad, and L Fratiglioni. "Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project." *American Journal of Epidemiology* 155.12 (2002): 1081-7.
278. Wilson, RS, CF Mendes De Leon, LL Barnes, JA Schneider, JL Bienias, DA Evans, and DA Bennett. "Participation in cognitively stimulating activities and risk of incident Alzheimer disease." *Journal of the American Medical Association* 287.6 (2002): 742-8.
279. LaRue, A, and LF Jarvik. "Cognitive function and prediction of dementia in old age." *International Journal of Aging and Human Development* 25.2 (1987): 79-89.
280. Laurin, D, R Verreault, J Lindsay, K MacPherson, and K Rockwood. "Physical activity and risk of cognitive impairment and dementia in elderly persons." *Archives of Neurology* 58.3 (2001).
281. Schaub, RT, H Münzberg, M Borchelt, R Nieczaj, T Hillen, FM Reischies, P Schlattmann, B Geiselman, and E Steinhagen-Thiessen. "Ventilatory capacity and risk for dementia." *The journals of gerontology, Series A, Biological sciences and medical sciences* 55.11 (2000): M677-M683.
282. Podewils, LJ, E Guallar, LH Kuller, LP Fried, OL Lopez, M Carlson, and CG Lyketsos. "Physical activity, APOE genotype, and dementia risk: findings from the cardiovascular health cognition study." *American Journal of Epidemiology* 161.7 (2005): 639-51.
283. Larson, EB, L Wang, JD Bowen, WC McCormick, L Teri, P Crane, and W Kukull. "Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older." *Annals of Internal Medicine* 144.2 (2006): 73-81.
284. Wilson, RS, DA Bennett, JL Bienias, NT Aggarwal, CF Mendes De Leon, MC Morris, JA Schneider, and DA Evans. "Cognitive activity and incident AD in a population-based sample of older persons." *Neurology* 59.12 (2002): 1910-4.
285. Verghese, J, RB Lipton, MJ Katz, CB Hall, CA Derby, G Kuslansky, AF Ambrose, M Sliwinski, and H Buschke. "Leisure activities and the risk of dementia in the elderly." *New England Journal of Medicine* 348 (2003): 2508-16.

-
286. Stern, Y, B Gurland, TK Tatemichi, MX Tang, D Wilder, and R Mayeux. "Influence of education and occupation on the incidence of Alzheimer's disease." *Journal of the American Medical Association* 271.13 (1994): 1004-10.
287. Yamada, M, F Kasagi, H Sasaki, N Masunari, Y Mimori, and G Suzuki. "Association between dementia and midlife risk factors: The Radiation Effects Research Foundation Adult Health Study." *Journal of the American Geriatric Society* 51.3 (2003): 410-4.
288. Abbott, RD, LR White, GW Ross, KH Masaki, JD Curb, and H Petrovitch. "Walking and dementia in physically capable elderly men." *Journal of the American Medical Association* 292.12 (2004): 1447-53.
289. Rovio, S, I K  reholt, EL Helkala, M Viitanen, B Winblad, J Tuomilehto, H Soininen, A Nissinen, and M Kivipelto. "Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease." *Lancet Neurology* 4.11 (2005): 705-11.
290. Andel, R, M Crowe, NL Pedersen, L Fratiglioni, B Johansson, and M Gatz. "Physical exercise at midlife and risk of dementia three decades later: a population-based study of Swedish twins." *The journals of gerontology, Series A, Biological sciences and medical sciences* 63.1 (2008): 62-6.
291. Taaffe, DR, F Irie, KH Masaki, RD Abbott, H Petrovitch, GW Ross, and LR White. "Physical activity, physical function, and incident dementia in elderly men: the Honolulu-Asia Aging Study." *The journals of gerontology, Series A, Biological sciences and medical sciences* 63.5 (2008): 529-35.
292. Rovio, S, I K  reholt, M Viitanen, B Winblad, J Tuomilehto, H Soininen, A Nissinen, and M Kivipelto. "Work-related physical activity and the risk of dementia and Alzheimer's disease." *International Journal of Geriatric Psychiatry* 22.9 (2007): 874-82.
293. Akbaraly, TN, F Portet, S Fustini, JF Dartigues, S Artero, O Rouaud, J Touchon, K Ritchie, and C Berr. "Leisure activities and the risk of dementia in the elderly: results from the Three-City Study." *Neurology* 73.11 (2009): 854-61.
294. Ravaglia, G, P Forti, A Lucicesare, N Pisacane, E Rietti, M Bianchin, and E Dalmonte. "Physical activity and dementia risk in the elderly: findings from a prospective Italian study." *Neurology* 70.19 Pt 2 (2008): 1786-94.

-
295. Prince, SA, KB Adamo, ME Hamel, J Hardt, S Connor Gorber, and M Tremblay. "A comparison of direct versus self-report measures for assessing physical activity levels in adults: a systematic review." *International Journal of Behavioral Nutrition and Physical Activity* 5 (2008): 56.
296. Podewils, LJ, E Guallar, LH Kuller, LP Fried, OL Lopez, M Carlson, and CG Lyketsos. "Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study." *American Journal of Epidemiology* 161.7 (2005): 639-51.
297. Mora, F, "Successful brain aging: plasticity, environmental enrichment, and lifestyle." *Dialogues in Clinical Neuroscience* 15.1 (2013): 45-52.
298. Helmer, C, D Damon, L Letenneur, C Fabrigoule, P Barberger-Gateau, S Lafont, R Fuhrer, T Antonucci, D Commenges, JM Orgogozo, and JF Dartigues. "Marital status and risk of Alzheimer's disease: a French population-based cohort study." *Neurology* 53.9 (1999):1953-8.
299. Wilson, RS, KR Krueger, SE Arnold, JA Schneider, JF Kelly, LL Barnes, Y Tang, and DA Bennett. "Loneliness and risk of Alzheimer disease." *Archives of General Psychiatry* 64.2 (2007): 234-40.
300. Hakansson, K, S Rovio, E-L Helkala, A-R Vilska, B Winblad, H Soininen, A Nissinen, AH Mohammed, and M Kivipelto. "Association between mid-life marital status and cognitive function in later life: population based cohort study." *British Medical Journal* 339 (2009): b2462.
301. Saczynski, JS, LA Pfeifer, K Masaki, ES Korf, D Laurin, L White, and LJ Launer. "The effect of social engagement on incident dementia: the Honolulu-Asia Aging Study." *American Journal of Epidemiology* 163.5 (2006): 433-40.
302. Fratiglioni, L, HX Wang, K Ericsson, M Maytan, and B Winblad. "Influence of social network on occurrence of dementia: a community based longitudinal study." *Lancet* 355.9212 (2000): 1315-19.
303. Sofi, F. "The Mediterranean diet revisited: evidence of its effectiveness grows." *Current Opinion in Cardiology* 24.5 (2009): 442-6.
304. Feart, C, C Samieri, and P Barberger-Gateau. "Mediterranean diet and cognitive function in older adults." *Current Opinion in Clinical Nutrition and Metabolic Care* 13.1 (2010): 14-8.
305. Nunomura, A, RJ Castellani, X Zhu, PI Moreira, G Perry, and MA Smith. "Involvement of oxidative stress in Alzheimer's disease." *Journal of Neuropathology and Experimental Neurology* 65.7 (2006): 631-41.

-
306. Pimentel, C, L Batista-Nascimento, C Rodrigues-Pousada, and RA Menezes. "Oxidative stress in Alzheimer's and Parkinson's diseases: insights from the yeast *Saccharomyces cerevisiae*." *Oxidative Medicine and Cellular Longevity* 2012 (2012).
307. Solfrizzi, V, F Panza, V Frisardi, D Seripa, G Logroscino, BP Imbimbo, and A Pilotto. "Diet and Alzheimer's disease risk factors or prevention: the current evidence." *Expert Review of Neurotherapeutics* 11.5 (2011): 677-708.
308. Mhatre, M, RA Floyd, and K Hensley. "Oxidative stress and neuroinflammation in Alzheimer's disease and amyotrophic lateral sclerosis: common links and potential therapeutic targets." *Journal of Alzheimer's Disease* 6.2 (2004): 147-57.
309. Layé, S, J-C Delpech, V De Smedt-Peyrusse, C Joffre, T Larrieu, C Madore, A Nadjar, and L Capuron. "Neuroinflammation and aging: influence of dietary n-3 polyunsaturated fatty acid." *OCL* 18.6 (2011): 301-6.
310. Chrysoshoou, C, DB Panagiotakos, C Pitsavos, UN Das, and C Stefanadis. "Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: the Attica study." *Journal of the American College of Cardiology* 44.1 (2004): 152-8.
311. Fragopoulou, E, DB Panagiotakos, C Pitsavos, M Tampourlou, C Chrysoshoou, T Nomikos, S Antonopoulou, and C Stefanadis. "The association between adherence to the Mediterranean diet and adiponectin levels among healthy adults: the ATTICA study." *The Journal of Nutritional Biochemistry* 21.4 (2010): 285-9.
312. Teixeira, AL, BS Diniz, AC Campos, AS Miranda, NP Rocha, LL Talib, WF Gattaz, and OV Forlenza. "Decreased levels of circulating adiponectin in mild cognitive impairment." *Neuromolecular Medicine* 15.1 (2013): 115-21.
313. Chan, K-H, K S-L Lam, O-Y Cheng, J S-C Kwan, P W-L Ho, K K-Y Cheng, SK Chung, J W-M Ho, VY Guo, and A Xu. "Adiponectin is protective against oxidative stress induced cytotoxicity in amyloid-beta neurotoxicity." *PLoSOne* 7.12 (2012): e52354.
314. Kamagawa, K, K Kohara, Y Tabara, E Uetani, T Nagai, M Yamamoto, M Igase, and T Miki. "Abdominal fat, adipose-derived hormones and mild cognitive impairment: The J-SHIP Study." *Dementia and Geriatric*

-
- Cognitive Disorders 30.5 (2010): 432-9.
315. van Himbergen, TM, AS Beiser, M Ai, S Seshadri, S Otokozawa, R Au, N Thongtang, PA Wolf, and EJ Schaefer. "Biomarkers for insulin resistance and inflammation and the risk for all-cause dementia and Alzheimer's disease: results from the Framingham Heart Study." *Archives of Neurology* 69.5 (2012): 594-600.
316. Chokkalingam, A, R Scherer, and K Dickersin. "Concordance of data between conference abstracts and full-reports [abstract]." *Sixth International Cochrane Colloquium* (1998).
317. Olsson, E, B Karlström, L Kilander, L Byberg, T Cederholm, and P Sjögren. "Dietary pattern and cognitive disorders in a 12-year follow-up study of 70 year old men." *Clinical Nutrition Supplements* 6.1 (2011): 209-10.
318. Gu, Y, JA Luchsinger, Y Stern, and N Scarmeas. "Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease." *Journal of Alzheimer's Disease* 22.2 (2010): 483-92.
319. Manly, JJ, N Schupf, MX Tang, and Y Stern. "Cognitive decline and literacy among ethnically diverse elders." *Journal of Geriatric Psychiatry and Neurology* 18.4 (2005): 213-17.
320. Sui, Z, LJ Moran, L Chapple, and JM Dodd. "Agreement between a food frequency questionnaire and the Willett questionnaire in overweight or obese pregnant women." *Journal of Nutritional Therapeutics* 2.2 (2013): 89-99.
321. Mackin, SR, and PA Areán. "Incidence and documentation of cognitive impairment among older adults with severe mental illness in a community mental health setting." *American Journal of Psychiatry* 17.1 (2009): 75-82.
322. Corkum, M, JA Hayden, G Kephart, R Urquhart, C Schlievert, and G Porter. "Screening for new primary cancers in cancer survivors compared to non-cancer controls: a systematic review and meta-analysis." *Journal of Cancer Survivorship* 7.3 (2013): 455-63.
323. Cherbuin, N, R Kumar, and K Anstey. "Caloric intake but not the mediterranean diet is associated with cognition and mild cognitive impairment." *Alzheimer's and Dementia* 7.4 (2011): S691.
324. Couto, E, S Sandin, M Lof, G Ursin, H-O Adami, and E Weiderpass. "Mediterranean dietary pattern and risk of breast cancer." *PLOS One* 8.2 (2013).

-
325. Richiardi, L, R Bellocco, and D Zugna. "Mediation analysis in epidemiology: interpretation and bias." *International Journal of Epidemiology* (2013): 1-9.
326. Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 271.
327. Bach-Faig, A, D Geleva, J Carrasco, L Ribas-Barba, and L Serra-Majem. "Evaluating associations between Mediterranean diet adherence indexes and biomarkers of diet and disease." *Public Health Nutrition* 9.8A (2006): 1110-7.
328. Rumawas, ME, JT Dwyer, NM McKeown, JB Meigs, G Rogers, and PF Jacques. The development of the Mediterranean-style dietary pattern score and its application to the American diet in the Framingham offspring cohort." *The Journal of Nutrition* 139.6 (2009): 1150-6.
329. Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 281.
330. Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 278.
331. Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 270.
332. Ayache, N. *Medical Image Computing and Computer-Assisted Intervention-Miccai 2012: 15th International Conference, Nice, France, October 1-5, 2012, Proceedings*. (Berlin: Springer, 2012) 136.
333. Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 300-301.
334. Moher, D, A Tsertsvadze, AC Tricco, M Eccles, J Grimshaw, M Sampson, and N Barrowman. "When and how to update systematic reviews." *Cochrane Database of Systematic Reviews* 23.1 (2008).
335. Dimsdale, JE. "Psychological stress and cardiovascular disease." *American College of Cardiology Foundation* 51.13 (2008): 1237-46.
336. Wilson, RS, DA Evans, JL Bienias, CF Mendes de Leon, JA Schneider, and DA Bennett. "Proneness to psychological distress is associated with risk of Alzheimer's disease." *Neurology* 61.11 (2003): 1479-85.

-
337. Wang, J. "Work stress as a risk factor for major depressive episodes." *Psychological Medicine* 35.6 (2005): 865-71.
338. Levenstein, S, MW Smith, and GA Kaplan. "Psychosocial predictors of hypertension in men and women." *Archives of Internal Medicine* 161.10 (2001): 1341-6.
339. Wilson, RS, DA Bennett, CF Mendes de Leon, JL Bienias, MC Morris, and DA Evans. "Distress proneness and cognitive decline in a population of older persons." *Psychoneuroendocrinology* 30.1 (2005): 11-7.
340. Sapolsky, RM, LC Krey, and BS McEwen. "The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis." *Endocrine Reviews* 7.3 (1986): 284-301.
341. Kopp, MS, and J Réthelyi. "Where psychology meets physiology: chronic stress and premature mortality—the Central-Eastern European health paradox." *Brain Research Bulletin* 62.5 (2004): 351367.
342. Keller, PA, A McCluskey, J Morgan, and SM O'connor. "The role of the HPA axis in psychiatric disorders and CRF antagonists as potential treatments." *Archiv der Pharmazie* 339.7 (2006): 346-55.
343. Johansson, L, X Guo, M Waern, S Östling, D Gustafson, C Bengtsson, and I Skoog. "Midlife psychological stress and risk of dementia: a 35-year longitudinal population study." *Brain* 133 (2010): 2217-24.
344. O'Brien, JT, I Schweitzer, D Ames, M Mastwyk, and P Colman. "The function of the hypothalamic-pituitary-adrenal axis in Alzheimer's disease. Response to insulin hypoglycaemia." *British Journal of Psychiatry* 165.5 (1994): 650-7.
345. Kiecolt-Glaser, JK, L McGuire, TF Robles, and R Glaser. "Psychoneuroimmunology and psychosomatic medicine: Back to the future." *Psychosomatic Medicine* 64.1 (2002):15–28.
346. Rissman, RA, MA Staup, AR Lee, NJ Justice, KC Rice, W Vale, and PE Sawchenko. "Corticotropin-releasing factor receptor-dependent effects of repeated stress on tau phosphorylation, solubility, and aggregation." *Proceedings of the National Academy of Sciences of the United States of America* 109.16 (2012): 6277-82.
347. Dong, H, B Goico, M Martin, CA Csernansky, A Bertchume, and JG Csernansky. "Modulation of hippocampal cell proliferation, memory, and amyloid plaque deposition in APPsw (Tg2576) mutant mice by isolation stress." *Neuroscience* 127.3 (2004): 601-9.

-
348. Kang, JE, JR Cirrito, H Dong, JG Csernansky, and DM Holtzman.. "Acute stress increases interstitial fluid amyloid-beta via corticotropin-releasing factor and neuronal activity." *Proceedings of the National Academy of Sciences of the United States of America* 104.25 (2007): 10673-8.
349. Tuppo, EE, and HR Arias. "The role of inflammation in Alzheimer's disease." *The International Journal of Biochemistry and Cell Biology* 37.2 (2005): 289-305.
350. Mark, GM, and AP Smith. "Stress models: a review and suggested new direction." In: Houdmont, J. and Leka, S. eds. *Occupational Health Psychology. European Perspectives On Research. Education and Practice*, vol. 3. (Nottingham: Nottingham University Press, 2008), 111-144.
351. Broome, A, and SP Llewelyn. *Health Psychology: Process and Applications*. (London: Chapman & Hall, 1995), 22.
352. Schneider, TR. "The role of neuroticism on psychological and physiological stress responses." *Journal of Experimental Psychology* 40.6 (2004): 795-804.
353. Gunther, KC, LH Cohen, and S Armeli. "The role of neuroticism in daily stress and coping." *Journal of Personality and Social Psychology* 77.5 (1999): 1087-1100.
354. Aleksandrova, LR, RP Souza, MR Bagby, DM Casey, DC Hodgins, GJ Smith, RJ Williams, DP Schopflocher, RT Wood, N el-Guebaly, JL Kennedy, and DSS Lobo. "Genetic underpinnings of neuroticism: a replication study." *Journal of Addiction Research and Therapy* 3.1 (2012).
355. Sherin, JE. "Post-traumatic stress disorder: the neurobiological impact of psychological trauma." *Dialogues in Clinical Neuroscience* 13.3 (2011): 263-78.
356. Andreasen, NC. "What is post-traumatic stress disorder?" *Dialogues in Clinical Neuroscience* 13.3 (2011): 240-3.
357. Stuber, ML, and E Shemesh. "Post-traumatic stress response to life-threatening illnesses in children and their parents." *Child and Adolescent Psychiatric Clinics of North America* 15.3 (2006): 597-609.
358. Dubois, B, HH Feldman, C Jacova, ST Dekosky, P Barberger-Gateau, J Cummings, A Delacourte, D Galasko, S Gauthier, G Jicha, K Meguro, J O'brien, F Pasquier, P Robert, M Rossor, S Salloway, Y Stern, PJ Visser, and P Scheltens. "Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria." *Lancet Neurology* 6.8 (2007): 734-46.

-
359. Reisberg, B. "Diagnostic criteria in dementia: a comparison of current criteria, research challenges, and implications for DSM-V." *Journal of Geriatric Psychiatry & Neurology* 19.3 (2006): 137-46.
360. Gallacher, J, A Bayer, M Fish, J Pickering, S Pedro, F Dunstan, S Ebrahim, and Y Ben-Shlomo. "Does anxiety affect risk of dementia? Findings from the Caerphilly prospective study." *Psychosomatic Medicine* 71.6 (2009): 659-66.
361. Wells, GA, B Shea, D O'Connell, J Peterson, V Welch, M Losos, and P Tugwell. "The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses."
<http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp>.
362. Tleyjeh, IM, T Kashour, FA Hakim, VA Zimmerman, PJ Erwin, AJ Sutton, and T Ibrahim. "Statins for the prevention and treatment of infections: a systematic review and meta-analysis." *Archives of Internal Medicine* 169.18 (2009): 1658-67.
363. Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 270.
364. Salmen, M, GA Ewy, and C Sasson. "Use of cardiocerebral resuscitation or AHA/ERC 2005 Guidelines is associated with improved survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis." *British Medical Journal* 2.5 (2012).
365. Wang, HX, M Wahlberg, A Karp, B Winblad, and L Fratiglioni. "Psychosocial stress at work is associated with increased dementia risk in late life." *Alzheimer's & Dementia* 8.2 (2012): 114-20.
366. Andel, R, M Crowe, EA Hahn, JA Mortimer, NL Pedersen, L Fratiglioni, B Johansson, and M Gatz. "Work-related stress may increase the risk of vascular dementia." *Journal of the American Geriatrics Society* 60.1 (2012): 60-7.
367. Yaffe, K, E Vittinghoff, K Lindquist, D Barnes, KE Covinsky, T Neylan, M Kluse, and C Marmar. "Posttraumatic stress disorder and risk of dementia among US veterans." *Archives of General Psychiatry* 67.6 (2010): 608-13.
368. Wilson, RS, LL Barnes, DA Bennett, Y Li, JL Bienias, CF Mendes de Leon, and DA Evans. "Proneness to psychological distress and risk of Alzheimer disease in a biracial community." *Neurology* 64.2 (2005): 380-2.

-
369. Wilson, RS, SE Arnold, JA Schneider, JF Kelly, Y Tang, and DA Bennett. "Chronic psychological distress and risk of Alzheimer's disease in old age." *Neuroepidemiology* 27.3 (2006): 143-53.
370. Wilson, RS, CT Begeney, PA Boyle, JA Schneider, and DA Bennett. "Vulnerability to stress, anxiety, and development of dementia in old age." *American Journal of Geriatric Psychiatry* 19.4 (2011): 327-34.
371. Duberstein, PR, BP Chapman, HA Tindle, KM Sink, P Bamonti, J Robbins, AF Jerant, and P Franks. "Personality and risk for Alzheimer's disease in adults 72 years of age and older: a 6-year follow-up." *Psychology & Aging* 26.2 (2011): 351-62.
372. Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 147.
373. Bredemeier, K, JM Spielberg, RL Sifton, H Berenbaum, W Heller, and GA Miller. "Screening for depressive disorders using the MASQ anhedonic depression scale: a receiver-operator characteristic analysis." *Psychological assessment* 22.3 (2010): 702-10.
374. Dynes, M, "Neuroticism and Emotion Regulation Success." Dissertation, Ohio State University, 2010, Web.
375. Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 268, 270.
376. *Neuroepidemiology: From Principles to Practice*. (Oxford: Oxford university press, 2004) 37.
377. Merrill, RM. *Introduction to Epidemiology*. (Sudbury, Mass: Jones and Bartlett Publishers, 2010) 171.
378. dos Santos Silva, I. "Chapter 9: Case-control studies." *Cancer Epidemiology: Principles and Methods*. Lyon: International Agency for Research on Cancer, 1999, <<http://www.iarc.fr/en/publications/pdfs-online/epi/cancerepi/CancerEpi-0.pdf>>. Web. 14. Oct. 2012, 194.
379. Nelson, KE, and CM William. *Infectious Disease Epidemiology: Theory and Practice*. (Sudbury, Mass: Jones and Bartlett Publishers, 2007) 85.
380. McKhan, G, D Drachman, M Folstein, R Katzman, D Price, and EM Stadlan. "Clinical Diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease." *Neurology* 34.7 (1984): 939-45.
381. Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 282.

-
- 382.Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 281.
- 383.Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 278.
- 384.dos Santos Silva, I. “Chapter 13: Interpretation of epidemiological studies.” *Cancer Epidemiology: Principles and Methods*, (Lyon: International Agency for Research on Cancer, 1999), <
<http://www.iarc.fr/en/publications/pdfs-online/epi/cancerepi/CancerEpi-13.pdf> >, Web, 25 Feb. 2013, 290.
- 385.Alzheimer’s Association. “Alzheimer’s Association Report: 2011 Alzheimer’s disease facts and figures.” *Alzheimer’s and Dementia* 7 (2011): 208-44.
- 386.Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 271, 364.
- 387.Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 271.
- 388.Aschengrau, A, and GR Seage. *Essentials of Epidemiology in Public Health*. (Sudbury, Mass: Jones and Bartlett Publishers, 2008) 272.
389. Truelsen, T, N Nielsen, G Boysen, and M Grønbaek. “Self-reported stress and risk of stroke: the Copenhagen City Heart Study.” *Stroke* 34.4 (2003): 856-62.
390. Gravely, AA, A Cutting, S Nugent, J Grill, K Carlson, and M Spoont. “Validity of PTSD diagnoses in VA administrative data: Comparison of VA administrative PTSD diagnoses to self-reported PTSD checklist scores.” *Journal of Rehabilitation Research and Development* 48.1 (2011): 21-30.
- 391.Wang, HX, A Karp, A Herlitz, M Crowe, I Kåreholt, B Winblad, and L Fratiglioni. “Personality and lifestyle in relation to dementia incidence.” *Neurology* 72.3 (2009): 253-9.
- 392.Storandt, M. “Cognitive deficits in the early stages of Alzheimer’s disease.” *Current Directions in Psychological Science* 17.3 (2008): 198-202.
- 393.McDonagh, M, K Peterson, P Raina, S Chang, and P Shekelle. “Avoiding Bias in Selecting Studies.Methods Guide for Comparative Effectiveness Reviews.” (Prepared by the Oregon Health & Science University, McMaster University, and Southern California Evidence-based Practice Centers under Contract No. 290-

-
- 2007-10057-I.)AHRQ Publication No. 13-EHC045-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2013. <www.effectivehealthcare.ahrq.gov/reports/final.cfm>.
394. Morrison, A, K Moulton, M Clark, J Polisena, M Fiander, M Mierzewski-Urban, S Mensinkai, T Clifford, and B Hutton. "English-language restriction when conducting systematic review-based meta-analyses: systematic review of published studies." Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.
395. "Knowledge Base." *KT Clearinghouse*. Web. 15 Oct. 2013.
396. Oxford Centre for Evidence-based Medicine, "Levels of Evidence." *Centre for Evidence Based Medicine*. University of Oxford, March 2009. Web. 15 Oct. 2013.
397. Moja, L, MP Fernandez del Rio, R Banzi, C Cusi, R D'Amico, A Liberati, G Lodi, E Lucenteforte, S Minozzi, V Pecoraro, G Virgili, and E Parmelli. "Multiple systematic reviews: methods for assessing discordances of results." *Internal and Emergency Medicine* 7 (2012): 563-8.
398. Hopayian, K. "The need for caution in interpreting high quality systematic reviews." *British Medical Journal* 323.7314 (2001): 681-4.
399. Siontis, KC, T Hernandez-Boussard, and JP Ioannidis. "Overlapping meta-analyses on the same topic: survey of published studies." *British Medical Journal* 347 (2013): f4501.
400. Sequeira-Byron, P, Z Fedorowicz, VA Jagannath, and MO Sharif. "An AMSTAR assessment of the methodological quality of systematic reviews of oral healthcare interventions published in the Journal of Applied Oral Science (JAOS)." *Journal of Applied Oral Science* 19.5 (2011): 440-7.
401. Breteler, MMB. "Vascular risk factors for Alzheimer's disease: an epidemiological perspective." *Neurobiology of Aging* 21.2 (2000): 153-160.
402. Murray, AD. *Imaging in Alzheimer's Disease and Other Dementias*. (Philadelphia: Saunders, 2012). Internet resource.
403. Public Health Agency of Canada. "The National Population Health Study of Neurological Conditions." Web. 23 Aug. 2012. 01 Nov. 2013.
404. Garritty, C, A Tsertsvadze, AC Tricco, M Sampson, and D Moher. "Updating systematic reviews: an international survey." *PLoS One* 5.4 (2010).

-
405. Bertram, L, MB McQueen, K Mullin, D Blacker, and RE Tanzi. "Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database." *Nature Genetics* 39.1 (2007): 17-23.
406. Weuve, J, MB McQueen, and D Blacker. The AlzRisk Database. Alzheimer Research Forum. Web. 01 October 2013. <<http://www.alzforum.org>>.
407. Graham, ID. "Knowledge synthesis and the Canadian Institutes of Health Research." *Systematic Reviews* 1 (2012): 6.
408. *PROSPERO – International prospective register of systematic reviews*. The University of York Centre for Reviews and Dissemination. 24 October 2013. Web. 30 October 2013. <<http://www.crd.york.ac.uk/prospero/prospero.asp>>.

APPENDICES

APPENDIX A-1: Literature Search Strategy

OVERVIEW	
Databases:	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations Ovid MEDLINE(R) Ovid EMBASE Classic + EMBASE Ovid PsycINFO PUBMED EBSCO CINAHL, EBSCO AARP Ageline HuGENET TOXLINE Cochrane Library Database of Abstracts of Reviews of Effects (DARE)
Date of Search:	September 22, 2011
Alerts:	Bi-weekly or weekly
Study Types:	Systematic reviews, meta-analyses
Limits:	Language limits: English or French Human population

SYNTAX GUIDE		
OVID		
AND	AND operator	Includes both terms
OR	OR operator	Includes either both, the one or the other term
/	Subject Heading	
.ab.	Abstract word	
.tw.	Text Word	Word in title or abstract field
.fs.	Floating subheading	Subheading of any Subject Heading
.pt.	Publication type	
.sh.	Subject Heading	
.mp.		Will search in title, abstract and in Subject Heading field
exp	Explode	Will include narrower terms to the Subject Heading being exploded
\$	Truncation/wild card	Adds non or more characters
\$n	Truncation/wild card	Adds non to <i>n</i> characters
?	Truncation/wild card	Adds non or one character
adj	Adjacency	Requires words are adjacent to each other in the order typed in
adjn	Adjacency	Requires words are adjacent with <i>n</i> words in between - regardless of word order
” – ”	Double quotation mark	Exact phrase searching
EBSCO		
MH	CINAHL Heading	

?	Wildcard	Replaces a single character
*	Truncation	Adds none or more characters
Nn	Near operator	N5 finds the words if they are within five words of one another regardless of word order
Wn	Within operator	W5 finds the words if they are within five words of one another and in the order typed in
“ _ “	Double quotation mark	Exact phrase searching
Cochrane Library		
AND	AND operator	Includes both terms
OR	OR operator	Includes either both, the one or the other term
MeSH descriptor	Subject Heading	
:ti	Title word	
:ab	Abstract word	
*	Truncation	Adds non or more characters
NEAR/n	NEAR operator	Requires words are adjacent with <i>n</i> words in between - regardless of word order
NEXT	NEXT operator	Requires words are adjacent to each other in the order typed in

Syntax Guide source: *The Cochrane Effective Practice and Organisation of Care (EPOC) Group, EPOC format for reporting the search process: Database Syntax Guide, The Cochrane Effective Practice and Organisation of Care (EPOC) Group, Web, 27 Sept. 2011, table.*

Template source: *Kaunelis, D. and Farrah, K. “Lecture: Introduction to Literature Searching.” Canadian Agency for Drugs and Technologies in Health (CADTH). University of Ottawa. 12 May 2011.*

Database: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process

Date of Search:	22 Sept. 2011 (Alerts until 31 Dec. 2011)
Years Searched:	1948 – 31 Dec. 2011
Alerts:	Bi-weekly
Limits:	Language (English, French) Human subjects
Filters:	Systematic review filter: Sikora, Lindsey. “Neurology Project – Alzheimer’s Disease.” Message to Mona Hersi. 16 May 2011. Email. Etiology/risk filter: Sikora, Lindsey. “Neurology Project – Alzheimer’s Disease.” Message to Mona Hersi. 16 May 2011. Email.
Search Strategy:	
Line #	Strategy
1	Meta-Analysis/
2	(meta anal* or metaanal*).ab,sh,ti.
3	1 or 2
4	(methodol* or systematic* or quantativ*).ab,sh,ti.
5	((methodol* or systematic* or quantativ*) adj review*) or overview* or survey*).ab,sh,ti.
6	review.pt,sh.
7	5 and 6
8	3 or 7
9	alzheimer disease/ or dementia/
10	(Alzheimer* or presenile dementia* or acute confusional senile dementia or Senile dementia* or primary senile degenerative dementia or primary degenerative senile).mp.
11	9 or 10
12	exp Risk/
13	Etiology.fs.
14	genetic.fs.
15	Prevention & control.fs.
16	12 or 13 or 14 or 15
17	11 and 16
18	limit 17 to humans
19	8 and 18
20	limit 19 to (english or french)

Database:	Ovid EMBASE Classic + EMBASE
Date of Search:	27 Sept. 2011 (Alerts until 31 Dec. 2011)
Years Searched:	1947 – 31 Dec. 2011
Alerts:	Bi-weekly
Limits:	Language (English, French) Human subjects
Filters:	Systematic review filter: InterTASC Information Specialists’s Sub-Group. “The InterTASC Information Specialists’ Sub-Group Search Filter Resource.” Web. 21 May 2011.
Search Strategy:	

Line #	Strategy
1	exp review/
2	(literature adj3 review\$).ti,ab.
3	exp meta analysis/
4	exp "Systematic Review"/
5	1 or 2 or 3 or 4
6	(medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab.
7	RETRACTED ARTICLE/
8	6 or 7
9	5 and 8
10	(systematic\$ adj2 (review\$ or overview)).ti,ab.
11	(meta?anal\$ or meta anal\$ or meta-anal\$ or metaanal\$ or metanal\$).ti,ab.
12	9 or 10 or 11
13	exp risk/
14	exp risk factor/
15	etiology/ or "general aspects of disease"/
16	"prevention and control"/
17	13 or 14 or 15 or 16
18	alzheimer disease/ or dementia/
19	Alzheimer*.mp.
20	18 or 19
21	17 and 20
22	limit 21 to human
23	12 and 22
24	limit 23 to (english or french)

Database:	Ovid PsycINFO
Date of Search:	22 Sept. 2011 (Alerts until 31 Dec. 2011)
Years Searched:	1806 – 31 Dec. 2011
Alerts:	Bi-weekly
Limits:	Language (English, French) Human subjects
Filters:	Systematic review filter: School of Public Health. "Search Filters for Ovid Medline, Ovid PsycINFO, and PubMed." <i>The University of Texas School of Public Health: Library</i>. The University of Texas Health Science Centre at Houston. 2010. Web. 21 May 2011. Etiology/Risk filter: Lamar Soutter Library. "PsycInfo Evidence-Based Filters." <i>Psychology/Psychiatry Evidence-Based Resources</i>. University of Massachusetts Medical School. 23 Aug. 2006. Web. 21 May 2011.
Search Strategy:	
Line #	Strategy
1	((systematic adj3 literature) or systematic review* or meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*)).ti,ab,id.
2	(cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of

	science").ab.
3	("systematic review" or "meta analysis").md. or ((review adj5 (rationale or evidence)).ti,ab. and "Literature Review".md.)
4	1 or 2 or 3
5	etiology.ti.
6	exp PREVENTION/
7	Epidemiolog\$.ti.
8	causal.ti.
9	cohort.ti.
10	empirical.ti.
11	risk.ti.
12	odds.ti.
13	case control.ti.
14	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	Dementia/ or Alzheimer's Disease/
16	(Alzheimer* or presenile dementia* or acute confusional senile dementia or Senile dementia* or primary senile degenerative dementia or primary degenerative senile).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
17	15 or 16
18	14 and 17
19	limit 18 to human
20	4 and 19
21	limit 20 to (english or french)

Database: PUBMED	
Date of Search:	22 Sept. 2011 (Alerts until 31 Dec. 2011)
Years Searched:	1951 – 31 Dec. 2011
Alerts:	Weekly
Limits:	Language (English, French) Human subjects
Filters:	Systematic review filter*: Health Information Research Unit. "Search Filters for MEDLINE in Ovid Syntax and the PubMed translation." <i>Health Information Research Unit: Evidence-Based Health Informatics</i>. McMaster University. Feb. 2011. Web. 21 May 2011. Etiology/Risk filter*: Health Information Research Unit. "Search Filters for MEDLINE in Ovid Syntax and the PubMed translation." <i>Health Information Research Unit: Evidence-Based Health Informatics</i>. McMaster University. Feb. 2011. Web. 21 May 2011. <i>*Both filters maximize specificity</i>
Search Strategy:	
Line #	Strategy
1	(Alzheimer Disease[MeSH Terms] OR Dementia[MeSH Terms] OR presenile dementia* OR acute confusional senile dementia OR Senile dementia* OR primary senile degenerative dementia OR primary degenerative senile)
2	MEDLINE[Title/Abstract] OR(systematic[Title/Abstract] AND review[Title/Abstract]) OR meta analysis[Publication Type]
3	(relative[Title/Abstract] AND risk*[Title/Abstract]) OR (relative risk[Text Word])

	OR risks[Text Word] OR cohort studies[MeSH:noexp] OR (cohort[Title/Abstract] AND stud*[Title/Abstract])
4	#1 AND #3
5	#4 AND #2

Database: EBSCO AARP Ageline	
Date of Search:	22 Sept. 2011 (Alerts until 31 Dec. 2011)
Years Searched:	1978 – 31 Dec. 2011
Alerts:	Bi-weekly
Limits:	None
Filters:	None
Search Strategy:	
Line #	Strategy
1	Alzheimer's Disease OR presenile dementia* OR acute confusional senile dementia OR Senile dementia* OR primary senile degenerative dementia OR primary degenerative senile
2	Meta-analysis OR Systematic review
3	risk factors OR causation OR etiology OR prevention and control
4	S1 and S3
5	S2 and S4

Database: EBSCO CINAHL	
Date of Search:	22 Sept. 2011 (Alerts until 31 Dec. 2011)
Years Searched:	1982 – 31 Dec. 2011
Alerts:	Bi-weekly
Limits:	None
Filters:	Systematic review filter: <i>Scottish Intercollegiate Guidelines Network (SIGN). "Search Filters."</i> Search Filters. Health Improvement Scotland. 16 Sept. 2011. Web. 21 May 2011. Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	(MH "Meta Analysis") or TX Meta analys\$ or TX Metaanaly\$
2	(MH "Literature Review+")
3	TX systematic review
4	TX systematic overview
5	PT commentary
6	PT letter
7	PT Editorial
8	(MH "Animals")
9	S1 or S2 or S3 or S4
10	S5 or S6 or S7 or S8
11	S9 not S10

12	(MH "Alzheimer's Disease") OR (MH "Dementia, Presenile") OR (MH "Dementia") OR (MH "Dementia, Senile") OR TX acute confusional senile dementia OR TX primary senile degenerative dementia OR TX primary degenerative senile
13	Dementia
14	S12 or S13
15	(MH "Risk Factors")
16	"causation"
17	"etiology"
18	"prevention and control"
19	S15 or S16 or S17 or S18
20	S14 AND S19
21	S20 AND S11

Database:	COCHRANE LIBRARY
Date of Search:	22 Sept. 2011 (Search re-run until 31 Dec. 2011)
Years Searched:	Inception – 31 Dec. 2011
Alerts:	None - Search updated until 31 Dec. 2011
Limits:	None
Filters:	Systematic review filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	MeSH descriptor Alzheimer Disease, this term only
2	MeSH descriptor Dementia explode all trees
3	(presenile dementia*) or (acute confusional senile dementia) or (Senile dementia*) or (primary senile degenerative dementia) or (primary degenerative senile)
4	(#1 OR #2 OR #3)
5	MeSH descriptor Risk Factors, this term only
6	MeSH descriptor Causality, this term only
7	Etiology
8	MeSH descriptor Risk, this term only
9	MeSH descriptor Primary Prevention, this term only
10	MeSH descriptor Risk Reduction Behaviour, this term only
11	(#5 OR #6 OR #7 OR #8 OR #9 OR #10)
12	(#4 AND #11)

Database:	DARE (Database of Abstracts of Reviews of Effects)
Date of Search:	28 Sept. 2011 (Search re-run until 31 Dec. 2011)
Years Searched:	Inception – 31 Dec. 2011
Alerts:	Weekly
Limits:	None
Filters:	Systematic review filter: None Etiology/Risk filter: None

Search Strategy:	
Line #	Strategy
1	MeSH DESCRIPTOR Alzheimer Disease EXPLODE ALL TREES
2	MeSH DESCRIPTOR Dementia EXPLODE ALL TREES
3	MeSH DESCRIPTOR Risk Factors EXPLODE ALL TREES
4	MeSH DESCRIPTOR Risk Reduction Behavior EXPLODE ALL TREES
5	(etiology) OR (causation) OR (primary prevention) IN DARE
6	#1 OR #2
7	#3 OR #4 OR #5
8	#6 AND #7

Database: TOXLINE	
Date of Search:	28 Sept. 2011 (Alerts until 31 Dec. 2011)
Years Searched:	1838 – 31 Dec. 2011
Alerts:	Monthly
Limits:	Language (English, French) Search “narrowed” by Publication Type (Review)
Filters:	Systematic review filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	(((((alzheimer) OR ((presenile dementia*) or (acute confusional senile dementia))) OR ((Senile dementia*) or (primary senile degenerative dementia))) OR primary degenerative senile) AND (Meta-Analysis or methodol* or systematic* or quantativ*)) AND (((risk or etiology) or (prevention and control)))

Database: HuGENet	
Date of Search:	22 Sept. 2011 (Search re-run until 31 Dec. 2011)
Years Searched:	2001 – 31 Dec. 2011
Alerts:	None – Search updated until 31 Dec. 2011
Limits:	None
Filters:	Database Specific Disease Filter: “Alzheimer Disease”, “Dementia” Database Specific Study Type Filter : “Meta-analysis”, “Pooled Analysis”, “HuGE Review”
Search Strategy:	
Line #	Strategy
1	alzheimer[Text+MeSH]>>Alzheimer's Disease, Dementia[Mesh]>>Meta-analysis, Pooled Analysis, HuGE Review[StudyType]

Database: ProQuest Dissertation and Theses	
Date of Search:	22 Sept. 2011 (Search re-run until 31 Dec. 2011)
Years Searched:	1861 – 31 Dec. 2011
Alerts:	Weekly
Limits:	Language (English, French)
Filters:	Systematic review filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	ab(alzheimer's disease OR presenile dementia OR acute confusional senile dementia OR senile dementia* or primary degenerative dementia OR primary degenerative senile) AND ab(((risk or etiology) OR causation)) AND ab(((systematic review or meta-analysis) OR review))

Database: Google	
Date of Search:	22 Sept. 2011 (Search re-run until 31 Dec. 2011)
Years Searched:	N/A
Alerts:	None – Search updated until 31 Dec. 2011
Limits:	None
Filters:	Systematic review filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	"Alzheimer's Disease" OR "presenile dementia" OR "acute confusional senile dementia" OR "Senile dementia" OR "primary senile degenerative dementia" OR "primary degenerative senile" AND "risk" OR "risk factor" OR "etiology" AND "systematic review"

Database: GoogleScholar	
Date of Search:	22 Sept. 2011 (Search re-run until 31 Dec. 2011)
Years Searched:	N/A
Alerts:	None – Search updated until 31 Dec. 2011
Limits:	None
Filters:	Systematic review filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	"Alzheimer's Disease" OR "presenile dementia" OR "acute confusional senile dementia" OR "Senile dementia" OR "primary senile degenerative dementia" OR "primary degenerative senile" AND "risk" OR "risk factor" OR "etiology" AND "systematic review"

Database:	American Journal of Alzheimer's Disease and Other Dementias (SAGE Journals Online)

Date of Search:	22 Sept. 2011 (Search re-run until 31 Dec. 2011)
Years Searched:	1986 – 31 Dec. 2011
Alerts:	Monthly
Limits:	None
Filters:	Systematic review filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	risk or etiology (in all fields) and systematic review or meta-analysis (in all fields)

Database:	International Journal of Alzheimer's Disease
Date of Search:	22 Sept. 2011 (Search re-run until 31 Dec. 2011)
Years Searched:	2009 – 31 Dec. 2011
Alerts:	None – Search updated until 31 Dec. 2011
Limits:	None
Filters:	Systematic review filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	No search engine available, therefore, all three volumes of the journal (2009, 2010, 2011) were scanned and articles under the “Review” heading in each volume were included.

APPENDIX A-2: AMSTAR Instrument

1. Was an ‘a priori’ design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can’t answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can’t answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can’t answer ☐ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can’t answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can’t answer ☐ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can’t answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? ‘A priori’ methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can’t answer ☐ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

Source: Shea BJ, et al. "AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews." *Journal of Clinical Epidemiology* 62.10 (2009): 1013-20.

APPENDIX A-3: Excluded studies (n=444) following full-article screening

Study	Reason for exclusion
Adelman S, Blanchard M and Livingston G. "A systematic review of the prevalence and covariates of dementia or relative cognitive impairment in the older African-Caribbean population in Britain." <i>International Journal of Geriatric Psychiatry</i> 24.7 (2009): 657-65.	AD was not an outcome/Risk estimates for AD not reported
Ahlskog JE, et al. "Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging." <i>Mayo Clinic Proceedings</i> 86.9 (2011): 876-84.	AD was not an outcome/Risk estimates for AD not reported
Akbaraly TN, et al. "Leisure activities and the risk of dementia in the elderly: results from the Three-City Study." <i>Neurology</i> 73.11 (2009): 854-61.	Not a systematic review
Akomolafe A, et al. "Genetic association between endothelial nitric oxide synthase and Alzheimer disease." <i>Clinical Genetics</i> 70.1 (2006): 49-56.	Not a systematic review
Albani, D., et al. "A novel study and meta-analysis of the genetic variation of the serotonin transporter promoter in the Italian population do not support a large effect on Alzheimer's disease risk." <i>International journal of Alzheimer's disease</i> 2011.(2011): 312341.	Not a systematic review
Albensi BC and Janigro D. "Traumatic brain injury and its effects on synaptic plasticity." <i>Brain Injury</i> 17.8 (2003): 653-63.	Not a systematic review
Allen M, et al. "Association and heterogeneity at the GAPDH locus in Alzheimer's disease." <i>Neurobiology of Aging</i> 33.1 (2012): 203.e25-33.	Not a systematic review
Alsina J. "Benefits of hormone replacement therapy--overview and update." <i>International Journal of Fertility & Womens Medicine</i> 42 Suppl 2.(1997): 329-46.	Not a systematic review
"Alzheimer's disease prevention: a reality check". <i>The Lancet Neurology</i> 9 (2010): 643.	Not a systematic review
Amadoruge PC and Barnham KJ. "Alzheimer's disease and metals: a review of the involvement of cellular membrane receptors in metallosignalling." <i>International journal of Alzheimer's disease</i> 2011.(2011): 542043.	Not a systematic review
Amantea D, et al. "From clinical evidence to molecular mechanisms underlying neuroprotection afforded by estrogens." <i>Pharmacological Research</i> 52.2 (2005): 119-32.	Not a systematic review
Ancelin ML and Berr C. "[Hormonal replacement therapy and Alzheimer's disease. All quiet on the western front?]." [in French] <i>Psychologie et Neuropsychiatrie du Vieillissement</i> 1.4 (2003): 251-7.	Not a systematic review
Ancelin ML and Ritchie K. "Lifelong endocrine fluctuations and related cognitive disorders." <i>Current Pharmaceutical Design</i> 11.32 (2005): 4229-52.	Not a systematic review
Antunez C., et al. Nitsch R.M., et al, eds. "Genetic association of CR1 polymorphism rs3818361 in Alzheimer's disease". Conference: 10th International Conference AD/PD - Alzheimer's and Parkinson's Diseases: Advances, Concepts and New Challenges Barcelona Spain. Conference Start: 20110309 Conference End: 20110313 Conference Publication: (var.pagings) <i>Neurodegenerative Diseases</i> 8.(2011).	Not a systematic review
Ariga T, Wakade C and Yu RK. "The pathological roles of ganglioside metabolism in Alzheimer's disease: effects of gangliosides on neurogenesis." <i>International journal of Alzheimer's disease</i> 2011.(2011): 193618.	Does not examine etiological risk factors
Aronow W.S. and Frishman W.H.. "Effects of antihypertensive drug treatment on cognitive function and the risk of dementia". <i>Clinical Geriatrics</i> 14.11 (2006): 25-28.	AD was not an outcome/Risk estimates for AD not reported
Arvanitakis Z, Wilson RS and Bennett DA. "Diabetes mellitus, dementia, and cognitive	Not a systematic review

function in older persons." <i>Journal of Nutrition, Health & Aging</i> 10.4 (2006): 287-91.	
Askarova S, Yang X and Lee JC. "Impacts of membrane biophysics in Alzheimer's disease: from amyloid precursor protein processing to a Peptide-induced membrane changes." <i>International journal of Alzheimer's disease</i> 2011.(2011): 134971.	Does not examine etiological risk factors
Athyros V.G., et al. "Homocysteine: An emerging cardiovascular risk factor that never really made it". <i>Open Clinical Chemistry Journal</i> 3.SPEC. ISSUE 1 (2010): 19-24.	Not a systematic review
Awad N, Gagnon M and Messier C. "The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function." <i>Journal of Clinical & Experimental Neuropsychology: Official Journal of the International Neuropsychological Society</i> 26.8 (2004): 1044-80.	AD was not an outcome/Risk estimates for AD not reported
Baghdasarian SB, Jneid H and Hoogwerf BJ. "Association of dyslipidemia and effects of statins on nonmacrovascular diseases." <i>Clinical Therapeutics</i> 26.3 (2004): 337-51.	Not a systematic review
Balk EM, et al. "Vitamin B6, B12, and folic acid supplementation and cognitive function: a systematic review of randomized trials." <i>Archives of Internal Medicine</i> 167.1 (2007): 21-30.	AD was not an outcome/Risk estimates for AD not reported
Ballard C, et al. "Alzheimer's disease." <i>Lancet</i> 377 (2011): 1019-31.	Not a systematic review
Baquer NZ, et al. "A metabolic and functional overview of brain aging linked to neurological disorders." <i>Biogerontology</i> 10.4 (2009): 377-413. Ovid MEDLINE(R). Web. 08 February. 2013.	Not a systematic review
Baron JA. "Beneficial effects of nicotine and cigarette smoking: the real, the possible and the spurious." <i>British Medical Bulletin</i> 52.1 (1996): 58-73.	Not a systematic review
Barrett-Connor E. "An introduction to obesity and dementia." <i>Current Alzheimer Research</i> 4.2 (2007): 97-101.	Not a systematic review
Bassil N. and Grossberg G.T.. "Evidence-based approaches to preventing Alzheimer's disease, part 1". <i>Primary Psychiatry</i> 16.6 (2009): 29-37.	Not a systematic review
Beffert U, Arguin C and Poirier J. "The polymorphism in exon 3 of the low density lipoprotein receptor-related protein gene is weakly associated with Alzheimer's disease." <i>Neuroscience Letters</i> 259.1 (1999): 29-32.	Not a systematic review
Bekris LM, et al. "Genetics of Alzheimer disease." <i>Journal of Geriatric Psychiatry & Neurology</i> 23.4 (2010): 213-27.	Not a systematic review
Belbin O, et al. "A multi-center study of ACE and the risk of late-onset Alzheimer's disease." <i>Journal of Alzheimer's Disease</i> 24.3 (2011): 587-97.	Not a systematic review
Belbin O, et al. "Investigation of 15 of the top candidate genes for late-onset Alzheimer's disease." <i>Human Genetics</i> 129.3 (2011): 273-82.	Not a systematic review
Belin AC, et al. "Association study of two genetic variants in mitochondrial transcription factor A (TFAM) in Alzheimer's and Parkinson's disease." <i>Neuroscience Letters</i> 420.3 (2007): 257-62.	Not a systematic review
Bendlin BB, et al. "Midlife predictors of Alzheimer's disease." <i>Maturitas</i> 65.2 (2010): 131-7.	Not a systematic review
Bent S and Ko R. "Commonly used herbal medicines in the United States: a review." <i>American Journal of Medicine</i> 116.7 (2004): 478-85.	Does not examine etiological risk factors
Bergmann C and Sano M. "Cardiac risk factors and potential treatments in Alzheimer's disease." <i>Neurological Research</i> 28.6 (2006): 595-604.	Not a systematic review
Berr C, Vercambre MN and Akbaraly TN. "[Epidemiology of Alzheimer's disease: methodological approaches and new perspectives]." [in French] <i>Psychologie et Neuropsychiatrie du Vieillissement</i> 7 Spec No 1.(2009): 7-14.	Not a systematic review
Bertram L. "Alzheimer's disease genetics current status and future perspectives." <i>International Review of Neurobiology</i> 84.(2009): 167-84.	Not a systematic review
Bertram L and Tanzi RE. "Thirty years of Alzheimer's disease genetics: the implications of systematic meta-analyses." <i>Nature Reviews Neuroscience</i> 9.10 (2008): 768-78.	Not a systematic review

Bertram L, et al. "The LDLR locus in Alzheimer's disease: a family-based study and meta-analysis of case-control data." <i>Neurobiology of Aging</i> 28.1 (2007): 18.e1-4.	Not a systematic review
Bertram L, et al. "Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database." <i>Nature Genetics</i> 39.1 (2007): 17-23.	Not a systematic review
Bertram L, et al. "Further evidence for LBP-1c/CP2/LSF association in Alzheimer's disease families." <i>Journal of Medical Genetics</i> 42.11 (2005): 857-62.	Not a systematic review
Bettens K., et al. "Meta-analysis of rare CLU variants shows association with alzheimer's risk and calls attention to the CLU betasubunit". Conference: Alzheimer's Association International Conference, AAIC 11 Paris France. Conference Start: 20110716 Conference End: 20110721 Conference Publication: (var.pagings) Alzheimer's and Dementia 7.4 SUPPL. 1 (2011): S93.	Not a systematic review
Biessels GJ, Deary IJ and Ryan CM. "Cognition and diabetes: a lifespan perspective." <i>Lancet Neurology</i> 7.2 (2008): 184-90.	Not a systematic review
Biessels GJ, et al. "Cognitive dysfunction and diabetes: implications for primary care." <i>Primary care diabetes</i> 1.4 (2007): 187-93.	Not a systematic review
Bird TD. "Genetic factors in Alzheimer's disease." <i>New England Journal of Medicine</i> 352.9 (2005): 862-4.	Not a systematic review
Birkenhager WH and Staessen JA. "Progress in cardiovascular diseases: cognitive function in essential hypertension." <i>Progress in Cardiovascular Diseases</i> 49.1 (2006): 1-10.	Not a systematic review
Birkenhager WH, Forette F and Staessen JA. "Dementia and antihypertensive treatment." <i>Current Opinion in Nephrology & Hypertension</i> 13.2 (2004): 225-30.	AD was not an outcome/Risk estimates for AD not reported
Birks J, Grimley EV and Van Dongen M. "Ginkgo biloba for cognitive impairment and dementia." <i>Cochrane Database of Systematic Reviews</i> 4 (2002): CD003120.	Does not examine etiological risk factors
Bisla J, et al. "Have we forgotten about dementia in care homes? The importance of maintaining survey research in this sector." <i>Age & Ageing</i> 40.1 (2011): 5-6.	AD was not an outcome/Risk estimates for AD not reported
Blomqvist ME, et al. "Towards compendia of negative genetic association studies: an example for Alzheimer disease." <i>Human Genetics</i> 119.1-2 (2006): 29-37.	AD was not an outcome/Risk estimates for AD not reported
Boada M, et al. "CALHM1 P86L polymorphism is associated with late-onset Alzheimer's disease in a recessive model." <i>Journal of Alzheimer's Disease</i> 20.1 (2010): 247-51.	Not a systematic review
Bobba A, et al. "Alzheimer's proteins, oxidative stress, and mitochondrial dysfunction interplay in a neuronal model of Alzheimer's disease." <i>International journal of Alzheimer's disease</i> 2010.(2010).	Does not examine etiological risk factors
Bonnefoy M, Drai J and Kostka T. "[Antioxidants to slow aging, facts and perspectives]." [in French] <i>Presse Medicale</i> 31.25 (2002): 1174-84.	Not a systematic review
Boothby LA and Doering PL. "Vitamin C and vitamin E for Alzheimer's disease." <i>Annals of Pharmacotherapy</i> 39.12 (2005): 2073-80.	Not a systematic review
Borenstein AR, Copenhaver CI and Mortimer JA. "Early-life risk factors for Alzheimer disease." <i>Alzheimer Disease & Associated Disorders</i> 20.1 (2006): 63-72.	Not a systematic review
Bourre JM. "[The role of nutritional factors on the structure and function of the brain: an update on dietary requirements]." [in French] <i>Revue Neurologique</i> 160.8-9 (2004): 767-92.	Not a systematic review
Brayne C, et al. "Challenges in the epidemiological investigation of the relationships between physical activity, obesity, diabetes, dementia and depression." <i>Neurobiology of Aging</i> 26 Suppl 1.(2005): 6-10.	Not a systematic review
Breitner J, et al. "ADAPT trial data." <i>American Journal of Medicine</i> 120.3 (2007): e3;	Not a systematic review

author reply e5; discussion e7.	
Breteler MM. "Vascular risk factors for Alzheimer's disease: an epidemiologic perspective." <i>Neurobiology of Aging</i> 21.2 (2000): 153-60.	Not a systematic review
Brouwers N, Sleegers K and Van Broeckhoven C. "Molecular genetics of Alzheimer's disease: an update." <i>Annals of Medicine</i> 40.8 (2008): 562-83.	Not a systematic review
Brown RC, Lockwood AH and Sonawane BR. "Neurodegenerative diseases: an overview of environmental risk factors." <i>Environmental Health Perspectives</i> 113.9 (2005): 1250-6.	Not a systematic review
Broyd SJ, et al. "Default-mode brain dysfunction in mental disorders: a systematic review." <i>Neuroscience & Biobehavioral Reviews</i> 33.3 (2009): 279-96.	Does not examine etiological risk factors
Bula C. "[Geriatrics]." [in French] <i>Revue Medicale Suisse</i> 2.47 (2006): 19, 21-4.	AD was not an outcome/Risk estimates for AD not reported
Burgess JD, et al. "Association of common KIBRA variants with episodic memory and AD risk." <i>Neurobiology of Aging</i> 32.3 (2011): 557.e1-9.	Not a systematic review
Bush A and Beail N. "Risk factors for dementia in people with down syndrome: issues in assessment and diagnosis." <i>American Journal of Mental Retardation</i> 109.2 (2004): 83-97.	Not a systematic review
Butt MS and Sultan MT. "Coffee and its consumption: benefits and risks." <i>Critical Reviews in Food Science & Nutrition</i> 51.4 (2011): 363-73.	Not a systematic review
Butterfield DA, Boyd-Kimball D and Castegna A. "Proteomics in Alzheimer's disease: insights into potential mechanisms of neurodegeneration." <i>Journal of Neurochemistry</i> 86.6 (2003): 1313-27.	Not a systematic review
Cai L, et al. "Genetic studies of A2M and BACE1 genes in Chinese Han Alzheimer's disease patients." <i>Neuroreport</i> 16.9 (2005): 1023-6.	Not a systematic review
Carrasquillo MM, et al. "Replication of EPHA1 and CD33 associations with late-onset Alzheimer's disease: a multi-centre case-control study." <i>Molecular Neurodegeneration</i> 6.1 (2011): 54.	Not a systematic review
Casserly I and Topol E. "Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins." <i>Lancet</i> 363.9415 (2004): 1139-46.	Not a systematic review
Cechetto DF, Hachinski V and Whitehead SN. "Vascular risk factors and Alzheimer's disease." <i>Expert Review of Neurotherapeutics</i> 8.5 (2008): 743-50.	Not a systematic review
Cedazo-Minguez A, Ismail MA and Mateos L. "Plasma cholesterol and risk for late-onset Alzheimer's disease." <i>Expert Review of Neurotherapeutics</i> 11.4 (2011): 495-8.	Not a systematic review
Chang C and Lin CH. "Hormone replacement therapy and menopause: a review of randomized, double-blind, placebo-controlled trials." <i>Kaohsiung Journal of Medical Sciences</i> 19.6 (2003): 257-70.	Does not examine etiological risk factors
Chen JH, Lin KP and Chen YC. "Risk factors for dementia." <i>Journal of the Formosan Medical Association</i> 108.10 (2009): 754-64.	Not a systematic review
Chiu HF and Zhang M. "Dementia research in China." <i>International Journal of Geriatric Psychiatry</i> 15.10 (2000): 947-53.	Not a systematic review
Chouliaras L, et al. "Gene-environment interaction research and transgenic mouse models of Alzheimer". <i>International Journal of Alzheimer's Disease</i> 2010 (2011).	Not a systematic review
Clarke R. "B-vitamins and prevention of dementia." <i>Proceedings of the Nutrition Society</i> 67.1 (2008): 75-81.	Not a systematic review
Clarke R, et al. "Effects of B-vitamins on plasma homocysteine concentrations and on risk of cardiovascular disease and dementia." <i>Current Opinion in Clinical Nutrition & Metabolic Care</i> 10.1 (2007): 32-9.	Not a systematic review
Coker LH and Shumaker SA. "Type 2 diabetes mellitus and cognition: an understudied issue in women's health." <i>Journal of Psychosomatic Research</i> 54.2 (2003): 129-39.	AD was not an outcome/Risk estimates

	for AD not reported
Combarros O, et al. "Epistasis in sporadic Alzheimer's disease." <i>Neurobiology of Aging</i> 30.9 (2009): 1333-49.	Not a systematic review
Combarros O, et al. "Interaction between interleukin-6 and intercellular adhesion molecule-1 genes and Alzheimer's disease risk." <i>Journal of Neurology</i> 252.4 (2005): 485-7.	Not a systematic review
Combarros O, et al. "The myeloperoxidase gene in Alzheimer's disease: a case-control study and meta-analysis." <i>Neuroscience Letters</i> 326.1 (2002): 33-6.	Not a systematic review
Combarros O, et al. "Age-dependent association between interleukin-1A (-889) genetic polymorphism and sporadic Alzheimer's disease. A meta-analysis." <i>Journal of Neurology</i> 250.8 (2003): 987-9.	Not a systematic review
Combarros O, et al. "Replication by the Epistasis Project of the interaction between the genes for IL-6 and IL-10 in the risk of Alzheimer's disease." <i>Journal of Neuroinflammation</i> 6.(2009): 22.	Not a systematic review
Cooper B. "Thinking preventively about dementia: a review." <i>International Journal of Geriatric Psychiatry</i> 17.10 (2002): 895-906.	Not a systematic review
Cornett, PF. <i>Risk Factors for Vascular Dementia</i> . Dissertation, University of North Texas, 2005. Web.	Not a systematic review
Corneveaux JJ, et al. "Association of CR1, CLU and PICALM with Alzheimer's disease in a cohort of clinically characterized and neuropathologically verified individuals." <i>Human Molecular Genetics</i> 19.16 (2010): 3295-301.	Not a systematic review
Counsell C. "Meta-analysis." <i>Practical Neurology</i> 3 (2003): 300-305.	AD was not an outcome/Risk estimates for AD not reported
Craig MC and Murphy DG. "Alzheimer's disease in women." <i>Best Practice & Research in Clinical Obstetrics & Gynaecology</i> 23.1 (2009): 53-61.	Not a systematic review
Crean S, et al. "Apolipoprotein E 4 prevalence in Alzheimer's disease patients varies across global populations: a systematic literature review and meta-analysis." <i>Dementia & Geriatric Cognitive Disorders</i> 31.1 (2011): 20-30. 31 (2011): #pages#	AD was not an outcome/Risk estimates for AD not reported
Croes EA, et al. "Octapeptide repeat insertions in the prion protein gene and early onset dementia." <i>Journal of Neurology, Neurosurgery & Psychiatry</i> 75.8 (2004): 1166-70.	AD was not an outcome/Risk estimates for AD not reported
Cucchiara B and Kasner SE. "Use of statins in CNS disorders." <i>Journal of the Neurological Sciences</i> 187.1-2 (2001): 81-9.	Not a systematic review
Cunnane SC, et al. "Fish, docosahexaenoic acid and Alzheimer's disease." <i>Progress in Lipid Research</i> 48.5 (2009): 239-56.	Not a systematic review
Cutler RG, et al. "Oxidative stress profiling: part II. Theory, technology, and practice." <i>Annals of the New York Academy of Sciences</i> 1055.(2005): 136-58.	Not a systematic review
Dartigues JF. "Epidemiology and prevalence of Alzheimer's disease and risk factors." <i>Psychogeriatrics</i> 4 (2004): 120-3.	Not a systematic review
Davignus ML, et al. "National Institutes of Health State-of-the-Science Conference statement: preventing alzheimer disease and cognitive decline." <i>Annals of Internal Medicine</i> 153.3 (2010): 176-81.	Not a systematic review
de la Torre JC. "Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics." <i>Lancet Neurology</i> 3.3 (2004): 184-90.	Not a systematic review
De Bresser J., et al. "Cerebral microinfarcts: A systematic review of neuropathological studies". Conference: Alzheimer's Association International Conference, AAIC 11 Paris France. Conference Start: 20110716 Conference End: 20110721 Conference Publication: (var.pagings) <i>Alzheimer's and Dementia</i> 7.4 SUPPL. 1 (2011): S699.	Publication could not be accessed
Deb S, et al. "APOE epsilon 4 influences the manifestation of Alzheimer's disease in	Not a systematic review

adults with Down's syndrome." <i>British Journal of Psychiatry</i> 176.(2000): 468-72.	
Deelen J, et al. "Genome-wide association study identifies a single major locus contributing to survival into old age; the APOE locus revisited." <i>Aging Cell</i> 10.4 (2011): 686-98.	Not a systematic review
Del Bo R, et al. "VEGF genetic variability is associated with increased risk of developing Alzheimer's disease." <i>Journal of the Neurological Sciences</i> 283.1-2 (2009): 66-8.	Not a systematic review
Delay C and Hebert SS. "MicroRNAs and Alzheimer's Disease Mouse Models: Current Insights and Future Research Avenues." <i>International journal of Alzheimer's disease</i> 2011.(2011): 894938.	Not a systematic review
DeMager PP, et al. "Pathological peptide folding in Alzheimer's disease and other conformational disorders." <i>Current Medicinal Chemistry</i> 9.19 (2002): 1763-80.	Not a systematic review
Deng Y, et al. "[Meta-analysis of the association of the LRP C766T polymorphism with the risk of Alzheimer's disease]." <i>Yi Chuan</i> 28.4 (2006): 393-8.	Not published in English or French
Dermaut B, et al. "Variable expression of presenilin 1 is not a major determinant of risk for late-onset Alzheimer's disease." <i>Journal of Neurology</i> 248.11 (2001): 935-9.	Not a systematic review
Di Biase L., et al. "Atrial fibrillation increases the risk of incident dementia: Evidence from a meta-analysis pasquale santangeli". Conference: American Heart Association's Scientific Sessions 2011 Orlando, FL United States. Conference Start: 20111112 Conference End: 20111116 Conference Publication: (var.pagings) <i>Circulation</i> 124.21 SUPPL. 1 (2011).	AD was not an outcome/Risk estimates for AD not reported
Dickstein DL, et al. "Role of vascular risk factors and vascular dysfunction in Alzheimer's disease." <i>Mount Sinai Journal of Medicine</i> 77.1 (2010): 82-102.	Not a systematic review
Diniz BS, Pinto Junior JA and Forlenza OV. "Do CSF total tau, phosphorylated tau, and beta-amyloid 42 help to predict progression of mild cognitive impairment to Alzheimer's disease? A systematic review and meta-analysis of the literature." <i>World Journal of Biological Psychiatry</i> 9.3 (2008): 172-82.	Does not examine etiological risk factors
Dinsdale HB, Robertson DM and Nag S. "Cerebral consequences of acute and chronic hypertension: an overview." <i>Clinical & Investigative Medicine - Medecine Clinique et Experimentale</i> 1.3-4 (1978): 181-90.	Not a systematic review
Dosunmu R, et al. "Environmental and dietary risk factors in Alzheimer's disease." <i>Expert Review of Neurotherapeutics</i> 7.7 (2007): 887-900.	Not a systematic review
Dunne L and Seaton TL. "Does hormone replacement therapy (HRT) improve cognitive function or either delay or prevent dementia in postmenopausal women?." <i>Journal of Family Practice</i> 50.6 (2001): 547.	AD was not an outcome/Risk estimates for AD not reported
Duron E and Hanon O. "Hypertension, cognitive decline and dementia." <i>Archives of cardiovascular diseases</i> 101.3 (2008): 181-9.	Not a systematic review
Dyall S.C.. "Amyloid-beta peptide, oxidative stress and inflammation in Alzheimer's disease: Potential neuroprotective effects of omega-3 polyunsaturated fatty acids". <i>International Journal of Alzheimer's Disease</i> (2010).	Not a systematic review
Eckert G.P., Muller W.E. and Wood W.G.. "Cholesterol-lowering drugs and Alzheimer's disease". <i>Future Lipidology</i> 2.4 (2007): 423-432.	Not a systematic review
Edhag O and Norlund A. "[Dementia diseases--a systematic review. SBU's summary and conclusions]." [in Swedish] <i>Lakartidningen</i> 103.28-29 (2006): 2135-9.	AD was not an outcome/Risk estimates for AD not reported
Edland SD, Slager S and Farrer M. "Genetic association studies in Alzheimer's disease research: challenges and opportunities." <i>Statistics in Medicine</i> 23.2 (2004): 169-78.	Not a systematic review
Ellisdon AM and Bottomley SP. "The role of protein misfolding in the pathogenesis of human diseases." <i>IUBMB Life</i> 56.3 (2004): 119-23.	Does not examine etiological risk factors
Elwood P, et al. "Aspirin for everyone older than 50? For." <i>BMJ</i> 330.7505 (2005):	Not a systematic review

1440-1.	
Emery J and Hayflick S. "The challenge of integrating genetic medicine into primary care." <i>BMJ</i> 322.7293 (2001): 1027-30.	Not a systematic review
Ernst E. "The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava." <i>Annals of Internal Medicine</i> 136.1 (2002): 42-53.	Does not examine etiological risk factors
Ershler WB and Keller ET. "Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty." <i>Annual Review of Medicine</i> 51.(2000): 245-70.	Not a systematic review
Etminan M, Gill S and Samii A. "The role of lipid-lowering drugs in cognitive function: a meta-analysis of observational studies." <i>Pharmacotherapy: The Journal of Human Pharmacology & Drug Therapy</i> 23.6 (2003): 726-30.	AD was not an outcome/Risk estimates for AD not reported
Evans GW. "The built environment and mental health." <i>Journal of Urban Health</i> 80.4 (2003): 536-55.	Does not examine etiological risk factors
Ezzo J. "From asthma to Alzheimer's: Cochrane vitamin reviews cover an array of topics." <i>Journal of Alternative & Complementary Medicine</i> 11.1 (2005): 213-6.	Not a systematic review
Fabiszewski KJ. "Alzheimer's disease: overview and progression." <i>Journal of Advanced Medical-Surgical Nursing</i> 1.2 (1989): 1-17.	Not a systematic review
Farquhar C, et al. "Long term hormone therapy for perimenopausal and postmenopausal women." <i>Cochrane Database of Systematic Reviews</i> 2 (2009): CD004143.	Does not examine etiological risk factors
Farrer LA, et al. "Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium." <i>JAMA</i> 278.16 (1997): 1349-56.	Not a systematic review
Feigin V, Ratnasabapathy Y and Anderson C. "Does blood pressure lowering treatment prevents dementia or cognitive decline in patients with cardiovascular and cerebrovascular disease?." <i>Journal of the Neurological Sciences</i> 229-230.(2005): 151-5.	AD was not an outcome/Risk estimates for AD not reported
Feki M, Souissi M and Mebazaa A. "[Vitamin E deficiency: risk factor in human disease?]." [in French] <i>Annales de Medecine Interne</i> 152.6 (2001): 398-406.	Not a systematic review
Ferreira IL, et al. "Multiple defects in energy metabolism in Alzheimer's disease." <i>Current Drug Targets</i> 11.10 (2010): 1193-206.	Not a systematic review
Finch CE. "Developmental origins of aging in brain and blood vessels: an overview." <i>Neurobiology of Aging</i> 26.3 (2005): 281-91.	Not a systematic review
Fisher D, et al. "Are infant size and growth related to burden of disease in adulthood? A systematic review of literature." <i>International Journal of Epidemiology</i> 35.5 (2006): 1196-210.	AD was not an outcome/Risk estimates for AD not reported
FitzGerald GA. "Cardiovascular pharmacology of nonselective nonsteroidal anti-inflammatory drugs and coxibs: clinical considerations." <i>American Journal of Cardiology</i> 89.6A (2002): 26D-32D.	AD was not an outcome/Risk estimates for AD not reported
Flicker L. "Modifiable lifestyle risk factors for Alzheimer's disease." <i>Journal of Alzheimer's Disease</i> 20.3 (2010): 803-11.	Not a systematic review
Flirski M and Sobow T. "Biochemical markers and risk factors of Alzheimer's disease." <i>Current Alzheimer Research</i> 2.1 (2005): 47-64.	Not a systematic review
Forbes D, et al. "Physical activity programs for persons with dementia." <i>Cochrane Database of Systematic Reviews</i> 3 (2008): CD006489.	Does not examine etiological risk factors
Ford GA, et al. "Stroke, dementia, and drug delivery." <i>British Journal of Clinical Pharmacology</i> 57.1 (2004): 15-26.	Does not examine etiological risk factors
Forette F and Hauw JJ. "[Treatment of Alzheimer's disease and future approaches]." [in French] <i>Therapie</i> 65.5 (2010): 429-37.	Does not examine etiological risk factors
Forstmeier S and Maercker A. "Potentially Modifiable Risk Factors in the Development of Alzheimer's Disease." <i>European Neurological Review</i> (2009).	Not a systematic review

Forsyth E and Ritzline PD. "An overview of the etiology, diagnosis, and treatment of Alzheimer disease." <i>Physical Therapy</i> 78.12 (1998): 1325-31.	Not a systematic review
Francotte P, et al. "New trends in the design of drugs against Alzheimer's disease." <i>Current Medicinal Chemistry</i> 11.13 (2004): 1757-78.	Does not examine etiological risk factors
Fratiglioni L, Mangialasche F and Qiu C. "Brain aging: lessons from community studies." <i>Nutrition Reviews</i> 68 Suppl 2.(2010): S119-27.	Not a systematic review
Frisardi V, et al. "Aluminum in the diet and Alzheimer's disease: from current epidemiology to possible disease-modifying treatment." <i>Journal of Alzheimer's Disease</i> 20.1 (2010): 17-30.	Not a systematic review
Froehlich TE, Bogardus ST Jr and Inouye SK. "Dementia and race: are there differences between African Americans and Caucasians?." <i>Journal of the American Geriatrics Society</i> 49.4 (2001): 477-84.	Not a systematic review
Fukumoto N., et al. "Sexually dimorphic effect of the Val66Met polymorphism of BDNF on susceptibility to Alzheimer's disease: New data and meta-analysis". <i>American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics</i> 153.1 (2010): 235-242.	Not a systematic review
Fusco D, et al. "Effects of antioxidant supplementation on the aging process." <i>Clinical Interventions In Aging</i> 2.3 (2007): 377-87.	Not a systematic review
Gacia M, et al. "Prion protein gene M129 allele is a risk factor for Alzheimer's disease." <i>Journal of Neural Transmission</i> 113.11 (2006): 1747-51.	Not a systematic review
Gallo JJ. "Epidemiology of mental disorders in middle age and late life: conceptual issues." <i>Epidemiologic Reviews</i> 17.1 (1995): 83-94.	Does not examine etiological risk factors
Gallo JJ and Lebowitz BD. "The epidemiology of common late-life mental disorders in the community: themes for the new century." <i>Psychiatric Services</i> 50.9 (1999): 1158-66.	Not a systematic review
Geldmacher DS. "Alzheimer disease prevention: focus on cardiovascular risk, not amyloid?." <i>Cleveland Clinic Journal of Medicine</i> 77.10 (2010): 689-704.	Not a systematic review
George DR, et al. "The role of nutrients in the prevention and treatment of Alzheimer's disease: methodology for a systematic review." <i>European Journal of Neurology</i> 16 Suppl 1.(2009): 8-11.	Not a systematic review
"Geriatrics. NSAIDs do not prevent Alzheimer's disease". <i>Nurses' Drug Alert</i> (2007): 32-3.	Not a systematic review
Gilleard C.J.. "Is Alzheimer's disease preventable? A review of two decades of epidemiological research". <i>Aging and Mental Health</i> 4.2 (2000): 101-118.	Not a systematic review
Gillette Guyonnet S, Andrieu S and Vellas B. "The potential influence of silica present in drinking water on Alzheimer's disease and associated disorders." <i>Journal of Nutrition, Health & Aging</i> 11.2 (2007): 119-24.	Not a systematic review
Gillette-Guyonnet S., et al. "Iana task force on nutrition and cognitive decline with aging". <i>Journal of Nutrition, Health and Aging</i> 11.2 (2007): 132-152.	Not a systematic review
Goldberg DM, Soleas GJ and Levesque M. "Moderate alcohol consumption: the gentle face of Janus." <i>Clinical Biochemistry</i> 32.7 (1999): 505-18.	AD was not an outcome/Risk estimates for AD not reported
Gorelick PB, et al. "Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association." <i>Stroke</i> 42.9 (2011): 2672-713.	Not a systematic review
Goumidi L, et al. "Study of thyroid hormone receptor alpha gene polymorphisms on Alzheimer's disease." <i>Neurobiology of Aging</i> 32.4 (2011): 624-30.	Not a systematic review
Grimley Evans J, Areosa Sastre A. Effect of the treatment of Type II diabetes mellitus on the development of cognitive impairment and dementia. <i>Cochrane Database of Systematic Reviews</i> 2003, Issue 1.Art.No.:CD003804.DOI: 10.1002/14651858.CD003804.	AD was not an outcome/Risk estimates for AD not reported

Grupe A, et al. "Evidence for novel susceptibility genes for late-onset Alzheimer's disease from a genome-wide association study of putative functional variants." <i>Human Molecular Genetics</i> 16.8 (2007): 865-73.	Not a systematic review
Hajjar I, Keown M and Frost B. "Antihypertensive agents for aging patients who are at risk for cognitive dysfunction." <i>Current Hypertension Reports</i> 7.6 (2005): 466-73.	Not a systematic review
Hall, AW. Predicting cognitive decline and dementia in elderly twins from indicators of early life oral health. Dissertation, University of Southern Carolina, 2009. Web.	Not a systematic review
Hammerstrom K. "Atypical antipsychotic drugs, dementia, and risk of death." <i>JAMA</i> 295.5 (2006): 496; author reply 496-7.	AD was not an outcome/Risk estimates for AD not reported
Hanger D.P. and Noble W.. "Functional implications of glycogen synthase kinase-3-mediated tau phosphorylation". <i>International Journal of Alzheimer's Disease</i> (2011).	Does not examine etiological risk factors
Harris JM, et al. "Human leucocyte antigen-A2 increases risk of Alzheimer's disease but does not affect age of onset in a Scottish population." <i>Neuroscience Letters</i> 294.1 (2000): 37-40.	Not a systematic review
Hartz AM and Bauer B. "ABC transporters in the CNS - an inventory." <i>Current Pharmaceutical Biotechnology</i> 12.4 (2011): 656-73.	Not a systematic review
Henderson AS and Jorm AF. "Is case-ascertainment of Alzheimer's disease in field surveys practicable?." <i>Psychological Medicine</i> 17.3 (1987): 549-55.	Does not examine etiological risk factors
Henderson ST. "High carbohydrate diets and Alzheimer's disease." <i>Medical Hypotheses</i> 62.5 (2004): 689-700.	Not a systematic review
Henderson VW. "Estrogens, episodic memory, and Alzheimer's disease: a critical update." <i>Seminars in Reproductive Medicine</i> 27.3 (2009): 283-93.	Not a systematic review
Hernan MA, Alonso A and Logroscino G. "Cigarette smoking and dementia: potential selection bias in the elderly." <i>Epidemiology</i> 19.3 (2008): 448-50.	Commentary, Editorial, Guideline, Case-study
Herrmann N. "Cognitive pharmacotherapy of Alzheimer's disease and other dementias." <i>Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie</i> 47.8 (2002): 715-22.	Does not examine etiological risk factors
Herrmann W. "Significance of hyperhomocysteinemia." <i>Clinical Laboratory</i> 52.7-8 (2006): 367-74.	Not a systematic review
Hodgkins PS. Reduced metal transferring binding in neurological disease. Dissertation, University of Aston in Birmingham, 1992. Web.	Not a systematic review
Hogervorst E and Bandelow S. "Sex steroids to maintain cognitive function in women after the menopause: a meta-analyses of treatment trials." <i>Maturitas</i> 66.1 (2010): 56-71.	AD was not an outcome/Risk estimates for AD not reported
Hogervorst E, et al. "The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis." <i>Neuroscience</i> 101.3 (2000): 485-512.	Not a systematic review
Hogervorst E, et al. "Measuring serum oestradiol in women with Alzheimer's disease: the importance of the sensitivity of the assay method." <i>European Journal of Endocrinology</i> 148.1 (2003): 67-72. (2003): 67-72.	Not a systematic review
Hollingworth P, et al. "Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease." <i>Nature Genetics</i> 43.5 (2011): 429-35.	Not a systematic review
Houlihan LM, et al. "Replication study of candidate genes for cognitive abilities: the Lothian Birth Cohort 1936." <i>Genes, Brain, & Behavior</i> 8.2 (2009): 238-47.	Not a systematic review
Hughes TM. Cholesterol metabolism in the brain and dementia." Dissertation, University of Pittsburgh, 2011. Web.	Publication could not be accessed
Ienco EC, et al. "May "mitochondrial eve" and mitochondrial haplogroups play a role in neurodegeneration and Alzheimer's disease?." <i>International journal of Alzheimer's disease</i> 2011.(2011): 709061.	Not a systematic review

Ikram MA, et al. "The GAB2 gene and the risk of Alzheimer's disease: replication and meta-analysis." <i>Biological Psychiatry</i> 65.11 (2009): 995-9.	Not a systematic review
Ineichen B. "The geography of dementia: an approach through epidemiology." <i>Health & Place</i> 4.4 (1998): 383-94.	Does not examine etiological risk factors
Janus C. "Vaccines for Alzheimer's disease: how close are we?." <i>CNS Drugs</i> 17.7 (2003): 457-74.	Not a systematic review
Jedrzejewski MK, Lee VM and Trojanowski JQ. "Lowering the risk of Alzheimer's disease: evidence-based practices emerge from new research." <i>Alzheimer's & Dementia</i> 1.2 (2005): 152-60.	Not a systematic review
Jellinger KA. "Traumatic brain injury as a risk factor for Alzheimer's disease." <i>Journal of Neurology, Neurosurgery & Psychiatry</i> 75.3 (2004): 511-2.	Not a systematic review
Jiwa NS, Garrard P and Hainsworth AH. "Experimental models of vascular dementia and vascular cognitive impairment: a systematic review." <i>Journal of Neurochemistry</i> 115.4 (2010): 814-28.	AD was not an outcome/Risk estimates for AD not reported
Jo SA, et al. "Association of BACE1 gene polymorphism with Alzheimer's disease in Asian populations: meta-analysis including Korean samples." <i>Dementia & Geriatric Cognitive Disorders</i> 25.2 (2008): 165-9.	Not a systematic review
Jun G, et al. "Meta-analysis confirms CR1, CLU, and PICALM as alzheimer disease risk loci and reveals interactions with APOE genotypes." <i>Archives of Neurology</i> 67.12 (2010): 1473-84.	Not a systematic review
Kalmijn S. "Fatty acid intake and the risk of dementia and cognitive decline: a review of clinical and epidemiological studies." <i>Journal of Nutrition, Health & Aging</i> 4.4 (2000): 202-7.	Not a systematic review
Kaminsky YG, et al. "Subcellular and metabolic examination of amyloid-beta peptides in Alzheimer disease pathogenesis: evidence for Abeta(25-35)." <i>Experimental Neurology</i> 221.1 (2010): 26-37.	Not a systematic review
Kanninen K, et al. "Targeting Glycogen Synthase Kinase-3 for Therapeutic Benefit against Oxidative Stress in Alzheimer's Disease: Involvement of the Nrf2-ARE Pathway." <i>International journal of Alzheimer's disease</i> 2011.(2011): 985085.	Not a systematic review
Kauwe JS, et al. "Alzheimer's disease risk variants show association with cerebrospinal fluid amyloid beta." <i>Neurogenetics</i> 10.1 (2009): 13-7.	Not a systematic review
Kawahara M. and Kato-Negishi M.. "Link between aluminum and the pathogenesis of Alzheimer's disease: The integration of the aluminum and amyloid cascade hypotheses". <i>International Journal of Alzheimer's Disease</i> (2011).	Not a systematic review
Keage HA, et al. "Risk for dementia and age at measurement." <i>International Journal of Geriatric Psychiatry</i> 26.3 (2011): 329-30.	Does not examine etiological risk factors
Kehoe PG, et al. "Haplotypes extending across ACE are associated with Alzheimer's disease." <i>Human Molecular Genetics</i> 12.8 (2003): 859-67.	Not a systematic review
Khachaturian ZS. "Overview of basic research on Alzheimer disease: implications for cognition." <i>Alzheimer Disease & Associated Disorders</i> 5 Suppl 1.(1991): S1-6.	Not a systematic review
Khanh Vinh Quoc Lu'o'ng and Lan Thi Hoàng Nguyen. "The Beneficial Role of Vitamin D in Alzheimers Disease". <i>American Journal of Alzheimer's Disease and Other Dementias</i> 26.7 (2011): 511-20.	Not a systematic review
Kidd PM. "A review of nutrients and botanicals in the integrative management of cognitive dysfunction." <i>Alternative Medicine Review</i> 4.3 (1999): 144-61.	Not a systematic review
Kim K.Y., Wood B.E. and Wilson M.I.. "Risk factors for Alzheimer's diseases: An overview for clinical practitioners". <i>Consultant Pharmacist</i> 20.3 (2005): 224-230.	Not a systematic review
Kim T, Hinton DJ and Choi DS. "Protein kinase C-regulated a production and clearance." <i>International journal of Alzheimer's disease</i> 2011.(2011): 857368.	Does not examine etiological risk factors
Klimkowicz-Mrowiec A, et al. "Paraoxonase gene polymorphism and the risk for	Not a systematic review

Alzheimer's disease in the polish population." <i>Dementia & Geriatric Cognitive Disorders</i> 31.6 (2011): 417-23.	
Koistinaho J, Malm T and Goldsteins G. "Glycogen synthase kinase-3: a mediator of inflammation in Alzheimer's disease?." <i>International journal of Alzheimer's disease</i> 2011.(2011): 129753.	Not a systematic review
Kolanowski AM. "An overview of the need-driven dementia-compromised behavior model." <i>Journal of Gerontological Nursing</i> 25.9 (1999): 7-9.	AD was not an outcome/Risk estimates for AD not reported
Kolsch H, et al. "ACE I/D polymorphism is a risk factor of Alzheimer's disease but not of vascular dementia." <i>Neuroscience Letters</i> 377.1 (2005): 37-9.	Not a systematic review
Kontush A. and Schekatolina S.. "An update on using vitamin E in Alzheimer's disease". <i>Expert Opinion on Drug Discovery</i> 3.2 (2008): 261-271.	Not a systematic review
Koster MN, et al. "The alpha2-macroglobulin gene in AD: a population-based study and meta-analysis." <i>Neurology</i> 55.5 (2000): 678-84.	Not a systematic review
Koyama A., et al. "Plasma amyloid-beta as a predictor of dementia and cognitive decline: A systematic review and meta-analysis". Conference: Alzheimer's Association International Conference, AAIC 11 Paris France. Conference Start: 20110716 Conference End: 20110721 Conference Publication: (var.pagings) Alzheimer's and Dementia 7.4 SUPPL. 1 (2011): S318.	Publication could not be accessed
Kraus AS and Forbes WF. "Aluminum, fluoride and the prevention of Alzheimer's disease." <i>Canadian Journal of Public Health. Revue Canadienne de Sante Publique</i> 83.2 (1992): 97-100.	Not a systematic review
Krause DL and Muller N. "Neuroinflammation, microglia and implications for anti-inflammatory treatment in Alzheimer's disease." <i>International journal of Alzheimer's disease</i> 2010.(2010)	Does not examine etiological risk factors
Kukull WA and Ganguli M. "Epidemiology of dementia: concepts and overview." <i>Neurologic Clinics</i> 18.4 (2000): 923-50.	Not a systematic review
Kuwano R, et al. "Dynamin-binding protein gene on chromosome 10q is associated with late-onset Alzheimer's disease." <i>Human Molecular Genetics</i> 15.13 (2006): 2170-82.	Not a systematic review
Lambert JC, et al. "The CALHM1 P86L polymorphism is a genetic modifier of age at onset in Alzheimer's disease: a meta-analysis study." <i>Journal of Alzheimer's Disease</i> 22.1 (2010): 247-55.	Not a systematic review
Lambert JC, et al. "Evidence of the association of BIN1 and PICALM with the AD risk in contrasting European populations." <i>Neurobiology of Aging</i> 32.4 (2011): 756.e11-5.	Not a systematic review
Lasher, Erin E. Changes in cognitive functioning associated with 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors: A theoretical reconciliation of disparate effects. Dissertation, University of Hartford, 2006. Web.	Not a systematic review
Launer LJ. "Diabetes and brain aging: epidemiologic evidence." <i>Current Diabetes Reports</i> 5.1 (2005): 59-63.	Not a systematic review
Lautenschlager NT, Cox K and Kurz AF. "Physical activity and mild cognitive impairment and Alzheimer's disease." <i>Current Neurology & Neuroscience Reports</i> 10.5 (2010): 352-8.	Not a systematic review
Leduc V, et al. "Function and comorbidities of apolipoprotein e in Alzheimer's disease." <i>International journal of Alzheimer's disease</i> 2011.(2011): 974361.	Not a systematic review
Lehmann DJ, et al. "Large meta-analysis establishes the ACE insertion-deletion polymorphism as a marker of Alzheimer's disease." <i>American Journal of Epidemiology</i> 162.4 (2005): 305-17.	Not a systematic review
Lehmann DJ, et al. "Using meta-analysis to explain the diversity of results in genetic studies of late-onset Alzheimer's disease and to identify high-risk subgroups." <i>Neuroscience</i> 108.4 (2001): 541-54.	Not a systematic review

Lei P, et al. "GSK-3 in Neurodegenerative Diseases." International journal of Alzheimer's disease 2011.(2011): 189246.	Not a systematic review
Leipzig RM. "That was the year that was: an evidence-based clinical geriatrics update." Journal of the American Geriatrics Society 46.8 (1998): 1040-9.	Not a systematic review
LePage, ML. Examination of relationships between participation in cognitive stimulating activities and leisure activities and dementia incidence. Dissertation, Trident University International, 2011. Web.	Not a systematic review
Leung G.T.Y. and Lam L.C.W.. "Leisure activities and cognitive impairment in late life - A selective literature review of longitudinal cohort studies". Hong Kong Journal of Psychiatry 17.3 (2007): 91-100.	Not a systematic review
Levey A, et al. "Mild cognitive impairment: an opportunity to identify patients at high risk for progression to Alzheimer's disease." Clinical Therapeutics 28.7 (2006): 991-1001.	Not a systematic review
Li Y, et al. "DAPK1 variants are associated with Alzheimer's disease and allele-specific expression." Human Molecular Genetics 15.17 (2006): 2560-8.	Not a systematic review
Li Y, et al. "Genetic association of the APP binding protein 2 gene (APBB2) with late onset Alzheimer disease." Human Mutation 25.3 (2005): 270-7.	Not a systematic review
Li Y, et al. "IL-10 -1082G/A polymorphism in Alzheimer's disease risk." Journal of the Neurological Sciences 309.1-2 (2011): 154-5.	Not a systematic review
Ligthart SA, et al. "Treatment of cardiovascular risk factors to prevent cognitive decline and dementia: a systematic review." Vascular Health & Risk Management 6.(2010): 775-85.	AD was not an outcome/Risk estimates for AD not reported
Linde K, et al. "Systematic reviews of herbal medicines--an annotated bibliography." Forschende Komplementarmedizin und Klassische Naturheilkunde 10 Suppl 1.(2003): 17-27.	Does not examine etiological risk factors
Liu F, et al. "A study of the SORL1 gene in Alzheimer's disease and cognitive function." Journal of Alzheimer's Disease 18.1 (2009): 51-64.	Not a systematic review
Liu J and Ames BN. "Reducing mitochondrial decay with mitochondrial nutrients to delay and treat cognitive dysfunction, Alzheimer's disease, and Parkinson's disease." Nutritional Neuroscience 8.2 (2005): 67-89.	Not a systematic review
Louis ED and Bennett DA. "Mild Parkinsonian signs: An overview of an emerging concept." Movement Disorders 22.12 (2007): 1681-8.	Not a systematic review
Low LF and Anstey KJ. "Hormone replacement therapy and cognitive performance in postmenopausal women--a review by cognitive domain." Neuroscience & Biobehavioral Reviews 30.1 (2006): 66-84.	AD was not an outcome/Risk estimates for AD not reported
Luchsinger JA. "Type 2 diabetes, related conditions, in relation and dementia: an opportunity for prevention?." Journal of Alzheimer's Disease 20.3 (2010): 723-36.	Not a systematic review
Luckhaus C and Sand PG. "Estrogen Receptor 1 gene (ESR1) variants in Alzheimer's disease. Results of a meta-analysis." Aging-Clinical & Experimental Research 19.2 (2007): 165-8.	Not a systematic review
Lye TC and Shores EA. "Traumatic brain injury as a risk factor for Alzheimer's disease: a review." Neuropsychology Review 10.2 (2000): 115-29.	Not a systematic review
Maki P and Hogervorst E. "The menopause and HRT. HRT and cognitive decline." Best Practice & Research Clinical Endocrinology & Metabolism 17.1 (2003): 105-22.	Not a systematic review
Maki PM. "A systematic review of clinical trials of hormone therapy on cognitive function: effects of age at initiation and progestin use." Annals of the New York Academy of Sciences 1052.(2005): 182-97.	AD was not an outcome/Risk estimates for AD not reported
Malchiodi-Albedi F, et al. "Amyloid oligomer neurotoxicity, calcium dysregulation, and lipid rafts." International journal of Alzheimer's disease 2011.(2011): 906964.	Does not examine etiological risk factors
Malouf R and Areosa Sastre A. "Vitamin B12 for cognition." Cochrane Database of	AD was not an

Systematic Reviews 3 (2003): CD004326.	outcome/Risk estimates for AD not reported
Malouf R. and Grimley Evans J.. "The effect of vitamin B6 on cognition". Cochrane database of systematic reviews (Online) 4 (2003): CD004393.	AD was not an outcome/Risk estimates for AD not reported
Malouf R and Grimley Evans J. "Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people." Cochrane Database of Systematic Reviews 4 (2008): CD004514.	AD was not an outcome/Risk estimates for AD not reported
Mancuso M, et al. "Mitochondria, cognitive impairment, and Alzheimer's disease." International journal of Alzheimer's disease 2009.(2009):	Not a systematic review
Manders M, et al. "Effectiveness of nutritional supplements on cognitive functioning in elderly persons: a systematic review." Journals of Gerontology Series A-Biological Sciences & Medical Sciences 59.10 (2004): 1041-9.	AD was not an outcome/Risk estimates for AD not reported
Manso Y, et al. "Copper modulation as a therapy for Alzheimer's disease?." International journal of Alzheimer's disease 2011.(2011): 370345.	Does not examine etiological risk factors
Manson JE and Martin KA. "Clinical practice. Postmenopausal hormone-replacement therapy." New England Journal of Medicine 345.1 (2001): 34-40.	Not a systematic review
Marrero MB, et al. "Application of alpha7 nicotinic acetylcholine receptor agonists in inflammatory diseases: an overview." Pharmaceutical Research 28.2 (2011): 413-6.	Does not examine etiological risk factors
Martin A, De Vivo G and Gentile V. "Possible role of the transglutaminases in the pathogenesis of Alzheimer's disease and other neurodegenerative diseases." International journal of Alzheimer's disease 2011.(2011): 865432.	Not a systematic review
Martin BK, et al. "The trialist, meta-analyst, and journal editor: lessons from ADAPT." American Journal of Medicine 120.3 (2007): 192-3.	Not a systematic review
Martinez A and Perez DI. "GSK-3 inhibitors: a ray of hope for the treatment of Alzheimer's disease?." Journal of Alzheimer's Disease 15.2 (2008): 181-91.	Not a systematic review
Martinez A, Gil C and Perez DI. "Glycogen synthase kinase 3 inhibitors in the next horizon for Alzheimer's disease treatment." International journal of Alzheimer's disease 2011.(2011): 280502.	Does not examine etiological risk factors
Martyn CN. "The epidemiology of Alzheimer's disease in relation to aluminium." Ciba Foundation Symposium 169.(1992): 69-79; discussion 79-86.	Not a systematic review
Maruszak A, et al. "The impact of mitochondrial and nuclear DNA variants on late-onset Alzheimer's disease risk." Journal of Alzheimer's Disease 27.1 (2011): 197-210.	Not a systematic review
Matsuzaki K. "Formation of Toxic Amyloid Fibrils by Amyloid -Protein on Ganglioside Clusters." International journal of Alzheimer's disease 2011.(2011): 956104.	Does not examine etiological risk factors
Mayeux R. "Clinical practice. Early Alzheimer's disease." New England Journal of Medicine 362.23 (2010): 2194-201.	Does not examine etiological risk factors
McConnell LM. "Understanding genetic testing for Alzheimer disease: medical and epidemiological background." Genetic Testing 3.1 (1999): 21-7.	Not a systematic review
McGeer PL and McGeer EG. "NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies." Neurobiology of Aging 28.5 (2007): 639-47.	Not a systematic review
McGeer PL, Schulzer M and McGeer EG. "Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies." Neurology 47.2 (1996): 425-32.	Not a systematic review
McGuinness B, et al. "Statins for the prevention of dementia." Cochrane Database of Systematic Reviews 2 (2009): CD003160.	AD was not an outcome/Risk estimates for AD not reported
McGuinness B, et al. "Systematic review: Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia." Journal of Neurology, Neurosurgery & Psychiatry 79.1 (2008): 4-5.	AD was not an outcome/Risk estimates for AD not reported

Mevel K, et al. "The default mode network in healthy aging and Alzheimer's disease." <i>International journal of Alzheimer's disease</i> 2011.(2011): 535816.	Does not examine etiological risk factors
Michelsen KA, Prickaerts J and Steinbusch HW. "The dorsal raphe nucleus and serotonin: implications for neuroplasticity linked to major depression and Alzheimer's disease." <i>Progress in Brain Research</i> 172.(2008): 233-64.	Not a systematic review
Mielke MM. Blood-related risk factors of vascular diseases and their relation to dementia and biomarkers of dementia. Dissertation, Johns Hopkins University, 2005. Web.	Not a systematic review
Mielke MM and Zandi PP. "Hematologic risk factors of vascular disease and their relation to dementia." <i>Dementia & Geriatric Cognitive Disorders</i> 21.5-6 (2006): 335-52.	Not a systematic review
Milionis HJ, Florentin M and Giannopoulos S. "Metabolic syndrome and Alzheimer's disease: a link to a vascular hypothesis?." <i>Cns Spectrums</i> 13.7 (2008): 606-13.	Not a systematic review
Miller JW. "Vitamin E and memory: is it vascular protection?." <i>Nutrition Reviews</i> 58.4 (2000): 109-11.	Not a systematic review
Minati L, et al. "Current concepts in Alzheimer's disease: a multidisciplinary review." <i>American Journal of Alzheimer's Disease & Other Dementias</i> 24.2 (2009): 95-121.	Not a systematic review
Mitchell AJ. "Depression as a risk factor for later dementia: a robust relationship?." <i>Age & Ageing</i> 34.3 (2005): 207-9.	Not a systematic review
Miu AC and Benga O. "Aluminum and Alzheimer's disease: a new look." <i>Journal of Alzheimer's Disease</i> 10.2-3 (2006): 179-201.	Not a systematic review
Mohamed A and Posse de Chaves E. "A internalization by neurons and glia." <i>International journal of Alzheimer's disease</i> 2011.(2011): 127984.	Not a systematic review
Mohan M, Bennett C and Carpenter PK. "Galantamine for dementia in people with Down syndrome." <i>Cochrane Database of Systematic Reviews</i> 1 (2009): CD007656.	Does not examine etiological risk factors
Mor F and Monsonogo A. "Immunization therapy in Alzheimer's disease." <i>Expert Review of Neurotherapeutics</i> 6.5 (2006): 653-9.	Not a systematic review
Morris JC. "Dementia update 2003." <i>Alzheimer Disease & Associated Disorders</i> 17.4 (2003): 245-58.	Not a systematic review
Morris MC. "The role of nutrition in Alzheimer's disease: epidemiological evidence." <i>European Journal of Neurology</i> 16 Suppl 1.(2009): 1-7.	Not a systematic review
Mowszowski L, Batchelor J and Naismith SL. "Early intervention for cognitive decline: can cognitive training be used as a selective prevention technique?." <i>International Psychogeriatrics</i> 22.4 (2010): 537-48.	Not a systematic review
Muangpaisan W, Brayne C and Alzheimer's Society Vascular Dementia Systematic Review Group. "Systematic review of statins for the prevention of vascular dementia or dementia." <i>Geriatrics & gerontology international</i> 10.2 (2010): 199-208.	AD was not an outcome/Risk estimates for AD not reported
Munn Z. "Review summaries: evidence for nursing practice. Physical leisure activities and their role in preventing dementia: a systematic review".	Not a systematic review
Murray LL, Ramage AE and Hopper A. "Memory impairments in adults with neurogenic communication disorders." <i>Seminars in Speech & Language</i> 22.2 (2001): 127-36.	Does not examine etiological risk factors
Mutter J, et al. "Does Inorganic Mercury Play a Role in Alzheimer's Disease? A Systematic Review and an Integrated Molecular Mechanism." <i>Journal of Alzheimer's Disease</i> 22 (2010): 357-74.	Does not examine etiological risk factors (does not report on incident AD)
Naderali EK, Ratcliffe SH and Dale MC. "Obesity and Alzheimer's disease: a link between body weight and cognitive function in old age." <i>American Journal of Alzheimer's Disease & Other Dementias</i> 24.6 (2009): 445-9.	Not a systematic review
Nagai M, Hoshida S and Kario K. "Hypertension and dementia." <i>American Journal of Hypertension</i> 23.2 (2010): 116-24.	Not a systematic review
Naj AC, et al. "Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are	Not a systematic review

associated with late-onset Alzheimer's disease." <i>Nature Genetics</i> 43.5 (2011): 436-41.	
Nakamura Y. "Regulating factors for microglial activation." <i>Biological & Pharmaceutical Bulletin</i> 25.8 (2002): 945-53.	Does not examine etiological risk factors
Narain Y, et al. "The ACE gene and Alzheimer's disease susceptibility." <i>Journal of Medical Genetics</i> 37.9 (2000): 695-7.	Not a systematic review
Neafsey EJ and Collins MA. "Moderate alcohol consumption and cognitive risk." <i>Neuropsychiatric Disease & Treatment</i> 7.(2011): 465-84.	Not a systematic review
Nelson J and Gutmann L. "Dementia: an overview." <i>West Virginia Medical Journal</i> 78.9 (1982): 219-25.	Does not examine etiological risk factors
"Newsbriefs". <i>American Journal of Alzheimer's Disease</i> 14 (1999): 5-8.	Not a systematic review
"Newsbriefs". <i>American Journal of Alzheimer's Disease and Other Dementias</i> 18.3 (2003): 133-4.	Not a systematic review
"Newsbriefs". <i>American Journal of Alzheimer's Disease and Other Dementias</i> 25.6 (2010): 532-7.	Not a systematic review
Nowotny P, et al. "Association studies between common variants in prolyl isomerase Pin1 and the risk for late-onset Alzheimer's disease." <i>Neuroscience Letters</i> 419.1 (2007): 15-7.	Not a systematic review
Ntais C and Polycarpou A. "Association of the endothelial nitric oxide synthase (NOS3) Glu298Asp gene polymorphism with the risk of Alzheimer's disease-- a meta-analysis." <i>Journal of Neurology</i> 252.10 (2005): 1276-8.	Not a systematic review
O'Donovan MC and Owen MJ. "Advances and retreats in the molecular genetics of major mental illness." <i>Annals of Medicine</i> 24.3 (1992): 171-7.	Not a systematic review
Oderfeld-Nowak B and Bacia A. "Expression of astroglial nerve growth factor in damaged brain." <i>Acta Neurobiologiae Experimentalis</i> 54.2 (1994): 73-80.	Does not examine etiological risk factors
Odle TG. "Alzheimer disease and other dementias." <i>Radiologic Technology</i> 75.2 (2003): 111-35; quiz 136-9.	Not a systematic review
Osuntokun BO, et al. "Epidemiology of age-related dementias in the Third World and aetiological clues of Alzheimer's disease." <i>Tropical & Geographical Medicine</i> 43.4 (1991): 345-51.	Not a systematic review
Otte C, et al. "A meta-analysis of cortisol response to challenge in human aging: importance of gender." <i>Psychoneuroendocrinology</i> 30.1 (2005): 80-91.	AD was not an outcome/Risk estimates for AD not reported
Qiu C. "Epidemiological findings of vascular risk factors in Alzheimer's disease: implications for therapeutic and preventive intervention." <i>Expert Review of Neurotherapeutics</i> 11.11 (2011): 1593-607.	Not a systematic review
Palacios S, et al. "The central nervous system and HRT." <i>International Journal of Fertility & Womens Medicine</i> 45.1 (2000): 13-21.	Not a systematic review
Panza F, et al. "Alcohol drinking, cognitive functions in older age, predementia, and dementia syndromes." <i>Journal of Alzheimer's Disease</i> 17.1 (2009): 7-31.	Not a systematic review
Panza F, et al. "Lipoproteins, vascular-related genetic factors, and human longevity." <i>Rejuvenation Research</i> 10.4 (2007): 441-58.	Not a systematic review
Panza F, et al. "Late-life depression, mild cognitive impairment, and dementia: possible continuum?." <i>American Journal of Geriatric Psychiatry</i> 18.2 (2010): 98-116.	Not a systematic review
Panza F, et al. "Metabolic syndrome and cognitive impairment: current epidemiology and possible underlying mechanisms." <i>Journal of Alzheimer's Disease</i> 21.3 (2010): 691-724.	Not a systematic review
Paradise M, Cooper C and Livingston G. "Systematic review of the effect of education on survival in Alzheimer's disease." <i>International Psychogeriatrics</i> 21.1 (2009): 25-32.	Does not examine etiological risk factors

Pary R, Tobias CR and Lippmann S. "Dementia: what to do." <i>Southern Medical Journal</i> 83.10 (1990): 1182-9. Ovid	Does not examine etiological risk factors
Pasinetti GM, et al. "Caloric intake, dietary lifestyles, macronutrient composition, and alzheimer' disease dementia." <i>International journal of Alzheimer's disease</i> 2011.(2011): 806293.	Not a systematic review
Patterson C, et al. "Diagnosis and treatment of dementia: 1. Risk assessment and primary prevention of Alzheimer disease." <i>CMAJ Canadian Medical Association Journal</i> 178.5 (2008): 548-56.	Not a systematic review
Pendlebury ST. "Stroke-related dementia: rates, risk factors and implications for future research." <i>Maturitas</i> 64.3 (2009): 165-71.	Not a systematic review
Pendlebury ST and Rothwell PM. "Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis." <i>Lancet Neurology</i> 8.11 (2009): 1006-18.	AD was not an outcome/Risk estimates for AD not reported
Perez-Lopez FR, et al. "Effects of the Mediterranean diet on longevity and age-related morbid conditions." <i>Maturitas</i> 64.2 (2009): 67-79. #	Not a systematic review
Peters R and Beckett N. "Hypertension, dementia, and antihypertensive treatment: implications for the very elderly." <i>Current Hypertension Reports</i> 11.4 (2009): 277-82.	AD was not an outcome/Risk estimates for AD not reported
Peters R, et al. "Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial." <i>Lancet Neurology</i> 7.8 (2008): 683-9.	Not a systematic review
Petit-Paitel A. "[GSK-3beta: a central kinase for neurodegenerative diseases?]." [in French] <i>M S-Medecine Sciences</i> 26.5 (2010): 516-21.	Not a systematic review
Piguet O and Garner B. "Vascular pharmacotherapy and dementia." <i>Current Vascular Pharmacology</i> 8.1 (2010): 44-50.	Not a systematic review
Plassman BL, et al. "Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life." <i>Annals of Internal Medicine</i> 153.3 (2010): 182-93.	AD was not an outcome/Risk estimates for AD not reported
Polidori MC. "Oxidative stress and risk factors for Alzheimer's disease: clues to prevention and therapy." <i>Journal of Alzheimer's Disease</i> 6.2 (2004): 185-91.	Not a systematic review
Polidori MC, Nelles G and Pientka L. "Prevention of dementia: focus on lifestyle." <i>International journal of Alzheimer's disease</i> 2010.(2010).	AD was not an outcome/Risk estimates for AD not reported
Price D. "Effect of NSAIDs on risk of Alzheimer's disease: conclusions on NSAIDs and Alzheimer's disease were overstated." <i>BMJ</i> 327.7417 (2003): 752.	Not a systematic review
Prince M, et al. "Leg length, skull circumference, and the prevalence of dementia in low and middle income countries: a 10/66 population-based cross sectional survey." <i>International Psychogeriatrics</i> 23.2 (2011): 202-13.	AD was not an outcome/Risk estimates for AD not reported
Pritchard A, et al. "Association study and meta-analysis of low-density lipoprotein receptor related protein in Alzheimer's disease." <i>Neuroscience Letters</i> 382.3 (2005): 221-6.	Not a systematic review
Purandare N. "Preventing dementia: role of vascular risk factors and cerebral emboli." <i>British Medical Bulletin</i> 91.(2009): 49-59.	Not a systematic review
Qian HR, Wang LN and Zhu MW. "[The relationship between prion protein gene codon 129 polymorphism and Alzheimer's disease]." <i>Chung-Hua Nei Ko Tsa Chih Chinese Journal of Internal Medicine</i> 45.11 (2006): 922-5.	Not a systematic review
Qiu C, De Ronchi D and Fratiglioni L. "The epidemiology of the dementias: an update." <i>Current Opinion in Psychiatry</i> 20.4 (2007): 380-5.	Not a systematic review
Quinn T.J., et al. "Association between circulating haemostatic measures and cognitive function or dementia - A systematic review and meta-analyses". Conference: 20th	AD was not an outcome/Risk estimates

European Stroke Conference, ESC 2011 Hamburg Germany. Conference Start: 20110524 Conference End: 20110527 Sponsor: Bayer, Boehringer, ev3, Allergan, Pfizer, et al. Conference Publication: (var.pagings) Cerebrovascular Diseases 31.(2011).	for AD not reported
Raber J, Huang Y and Ashford JW. "ApoE genotype accounts for the vast majority of AD risk and AD pathology." <i>Neurobiology of Aging</i> 25.5 (2004): 641-50.	Not a systematic review
Radak Z, et al. "Exercise plays a preventive role against Alzheimer's disease." <i>Journal of Alzheimer's Disease</i> 20.3 (2010): 777-83.	Not a systematic review
Rapoport MJ and Feinstein A. "Outcome following traumatic brain injury in the elderly: a critical review." <i>Brain Injury</i> 14.8 (2000): 749-61.	Not a systematic review
Rasouri S, Lagouge M and Auwerx J. "[SIRT1/PGC-1: a neuroprotective axis?]." [in French] <i>M S-Medecine Sciences</i> 23.10 (2007): 840-4.	Not a systematic review
Readnower RD, Sauerbeck AD and Sullivan PG. "Mitochondria, Amyloid , and Alzheimer's Disease." <i>International journal of Alzheimer's disease</i> 2011.(2011): 104545.	Not a systematic review
Ready RE, et al. "Apolipoprotein E-e4, processing speed, and white matter volume in a genetically enriched sample of midlife adults." <i>American Journal of Alzheimer's Disease & Other Dementias</i> 26.6 (2011): 463-8.	Not a systematic review
Reiss AB. "Cholesterol and apolipoprotein E in Alzheimer's disease." <i>American Journal of Alzheimer's Disease & Other Dementias</i> 20.2 (2005): 91-6.	Not a systematic review
Reitz C, Brayne C and Mayeux R. "Epidemiology of Alzheimer disease." <i>Nature Reviews Neurology</i> 7.3 (2011): 137-52.	Not a systematic review
Reitz C, et al. "SORCS1 alters amyloid precursor protein processing and variants may increase Alzheimer's disease risk." <i>Annals of Neurology</i> 69.1 (2011): 47-64.	Not a systematic review
Resnick SM and Henderson VW. "Hormone therapy and risk of Alzheimer disease: a critical time." <i>JAMA</i> 288.17 (2002): 2170-2.	Not a systematic review
Rifat SL. "Graphic representations of effect estimates: an example from a meta-analytic review." <i>Journal of Clinical Epidemiology</i> 43.11 (1990): 1267-9.	Not a systematic review
Ritchie K and Kildea D. "Is senile dementia "age-related" or "ageing-related"?--evidence from meta-analysis of dementia prevalence in the oldest old." <i>Lancet</i> 346.8980 (1995): 931-4.	AD was not an outcome/Risk estimates for AD not reported
Ritchie K, Kildea D and Robine JM. "The relationship between age and the prevalence of senile dementia: a meta-analysis of recent data." <i>International Journal of Epidemiology</i> 21.4 (1992): 763-9.	Not a systematic review
Robbins TW, Elliott R and Sahakian BJ. "Neuropsychology--dementia and affective disorders." <i>British Medical Bulletin</i> 52.3 (1996): 627-43.	Does not examine etiological risk factors
Rocca WA. "Frequency, distribution, and risk factors for Alzheimer's disease." <i>Nursing Clinics of North America</i> 29.1 (1994): 101-11.	Not a systematic review
Rocca WA, et al. "Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause." <i>Neurology</i> 69.11 (2007): 1074-83.	AD was not an outcome/Risk estimates for AD not reported
Rockwood K. "Epidemiological and clinical trials evidence about a preventive role for statins in Alzheimer's disease." <i>Acta Neurologica Scandinavica. Supplementum</i> 185.(2006): 71-7.	Not a systematic review
Rockwood K and Darvesh S. "The risk of dementia in relation to statins and other lipid lowering agents." <i>Neurological Research</i> 25.6 (2003): 601-4.	Not a systematic review
Rodda J, Walker Z and Carter J. "Depression in older adults." <i>BMJ</i> 343.(2011): d5219.	Does not examine etiological risk factors
Rogers J. "The inflammatory response in Alzheimer's disease." <i>Journal of Periodontology</i> 79.8 Suppl (2008): 1535-43.	Does not examine etiological risk factors
Rosenthal TC and Khotianov N. "Managing Alzheimer dementia tomorrow." <i>Journal of</i>	Does not examine

the American Board of Family Practice 16.5 (2003): 423-34.	etiological risk factors
Rubinsztein DC, et al. "Apo E genotypes and risk of dementia in Down syndrome." American Journal of Medical Genetics 88.4 (1999): 344-7.	Not a systematic review
Russ C, et al. "The microtubule associated protein Tau gene and Alzheimer's disease--an association study and meta-analysis." Neuroscience Letters 314.1-2 (2001): 92-6.	Not a systematic review
Ruxton C, et al. "The health benefits of omega-3 polyunsaturated fatty acids: a review of the evidence." Journal of Human Nutrition & Dietetics 20.3 (2007): 275-85.	Not a systematic review
Ryan J, et al. "Hormonal treatment, mild cognitive impairment and Alzheimer's disease." International Psychogeriatrics 20.1 (2008): 47-56.	Not a systematic review
Sachdev PS. "Alzheimer disease: homocysteine and alzheimer disease: an intervention study." Nature Reviews Neurology 7.1 (2011): 9-10.	Not a systematic review
Salerno-Kennedy R and Cashman KD. "The role of nutrition in dementia: an overview." Journal of the British Menopause Society 12.2 (2006): 44-8.	Not a systematic review
Salerno-Kennedy R and Cashman KD. "Relationship between dementia and nutrition-related factors and disorders: an overview." International Journal for Vitamin & Nutrition Research 75.2 (2005): 83-95.	Not a systematic review
Sanchez-Guerra M, et al. "Case-control study and meta-analysis of low density lipoprotein receptor-related protein gene exon 3 polymorphism in Alzheimer's disease." Neuroscience Letters 316.1 (2001): 17-20.	Not a systematic review
Sano M. "Current concepts in the prevention of Alzheimer's disease." Cns Spectrums 8.11 (2003): 846-53.	Not a systematic review
Sano M. "Understanding the role of estrogen on cognition and dementia." Journal of Neural Transmission. Supplementum 59.(2000): 223-9.	Not a systematic review
Sarajarvi T, et al. "An association study of 21 potential Alzheimer's disease risk genes in a Finnish population." Journal of Alzheimer's Disease 21.3 (2010): 763-7.	Not a systematic review
Sastre M, Klockgether T and Heneka MT. "Contribution of inflammatory processes to Alzheimer's disease: molecular mechanisms." International Journal of Developmental Neuroscience 24.2-3 (2006): 167-76.	Not a systematic review
Savica R and Petersen RC. "Prevention of dementia." Psychiatric Clinics of North America 34.1 (2011): 127-45.	Not a systematic review
Savory J, et al. "Can the controversy of the role of aluminum in Alzheimer's disease be resolved? What are the suggested approaches to this controversy and methodological issues to be considered?." Journal of Toxicology & Environmental Health 48.6 (1996): 615-35.	Not a systematic review
Savva GM, Stephan BC and Alzheimer's Society Vascular Dementia Systematic Review Group. "Epidemiological studies of the effect of stroke on incident dementia: a systematic review." Stroke 41.1 (2010): e41-6.	AD was not an outcome/Risk estimates for AD not reported
Scacchi R, et al. "Screening of two mutations at exon 3 of the apolipoprotein E gene (sites 28 and 42) in a sample of patients with sporadic late-onset Alzheimer's disease." Neurobiology of Aging 24.2 (2003): 339-43. #journal# 24 (2003): #pages#	Not a systematic review
Schjeide BM, et al. "The role of clusterin, complement receptor 1, and phosphatidylinositol binding clathrin assembly protein in Alzheimer disease risk and cerebrospinal fluid biomarker levels." Archives of General Psychiatry 68.2 (2011): 207-13.	Not a systematic review
Schjeide BM, et al. "Assessment of Alzheimer's disease case-control associations using family-based methods." Neurogenetics 10.1 (2009): 19-25.	Not a systematic review
Schneider JA, Tangney CC and Morris MC. "Folic acid and cognition in older persons." Expert Opinion on Drug Safety 5.4 (2006): 511-22.	Not a systematic review
Schoneich C. "Redox processes of methionine relevant to beta-amyloid oxidation and Alzheimer's disease." Archives of Biochemistry & Biophysics 397.2 (2002): 370-6.	Does not examine etiological risk factors

Schutte DL and Holston EC. "Chronic dementing conditions, genomics, and new opportunities for nursing interventions." <i>Journal of Nursing Scholarship</i> 38.4 (2006): 328-34.	Not a systematic review
Schuur M, et al. "Cathepsin D gene and the risk of Alzheimer's disease: a population-based study and meta-analysis." <i>Neurobiology of Aging</i> 32.9 (2011): 1607-14.	Not a systematic review
Schwartz BS and Stewart WF. "Lead and cognitive function in adults: a questions and answers approach to a review of the evidence for cause, treatment, and prevention." <i>International Review of Psychiatry</i> 19.6 (2007): 671-92.	AD was not an outcome/Risk estimates for AD not reported
Seshadri S.. "Genetic studies of alzheimer's disease". Conference: Alzheimer's Association International Conference, AAIC 11 Paris France. Conference Start: 20110716 Conference End: 20110721 Conference Publication: (var.pagings) Alzheimer's and Dementia 7.4 SUPPL. 1 (2011): S83.	Not a systematic review
Seshadri S, et al. "Genome-wide analysis of genetic loci associated with Alzheimer disease." <i>JAMA</i> 303.18 (2010): 1832-40.	Not a systematic review
Sheinerman KS. From WW domain of neuronal protein Fe65 to signaling network of Alzheimer's amyloid precursor protein. Dissertation, New York University, 2000. Web.	Does not examine etiological risk factors
Shi H, et al. "Analysis of Genome-Wide Association Study (GWAS) data looking for replicating signals in Alzheimer's disease (AD)." <i>International Journal of Molecular Epidemiology and Genetics</i> 1.1 (2010): 53-66.	Not a systematic review
Shih RA, et al. "Cumulative lead dose and cognitive function in adults: a review of studies that measured both blood lead and bone lead." <i>Environmental Health Perspectives</i> 115.3 (2007): 483-92.	AD was not an outcome/Risk estimates for AD not reported
Shobab LA, Hsiung GY and Feldman HH. "Cholesterol in Alzheimer's disease." <i>Lancet Neurology</i> 4.12 (2005): 841-52.	Not a systematic review
"Short reports. Herbal medicine". <i>Focus on Alternative & Complementary Therapies</i> 13.3 (2008): 206-7.	AD was not an outcome/Risk estimates for AD not reported
Sims R., et al. "Does variation in mitochondrial haplogroups associate with Alzheimer's disease?". Conference: Alzheimer's Association International Conference, AAIC 11 Paris France. Conference Start: 20110716 Conference End: 20110721 Conference Publication: (var.pagings) Alzheimer's and Dementia 7.4 SUPPL. 1 (2011): S195-S196.	Not a systematic review
Small BJ, et al. "Apolipoprotein E and cognitive performance: a meta-analysis." <i>Psychology & Aging</i> 19.4 (2004): 592-600.	AD was not an outcome/Risk estimates for AD not reported
Smith MA, Petot GJ and Perry G. "Diet and oxidative stress: a novel synthesis of epidemiological data on Alzheimer's disease." <i>Journal of Alzheimer's Disease</i> 1.4-5 (1999): 203-6.	Not a systematic review
Sobow T. and Kloszewska I.. "Cholinesterase inhibitors in mild cognitive impairment: A meta-analysis of randomized controlled trials". <i>Neurologia i Neurochirurgia Polska</i> 41.1 (2007): 13-21.	AD was not an outcome/Risk estimates for AD not reported
Sofi F, et al. "Effectiveness of the Mediterranean diet: can it help delay or prevent Alzheimer's disease?." <i>Journal of Alzheimer's Disease</i> 20.3 (2010): 795-801.	Not a systematic review
Solfrizzi V, et al. "Moderate alcohol consumption, apolipoprotein E, and neuroprotection." <i>Archives of Neurology</i> 66.4 (2009): 541-2.	Not a systematic review
Solfrizzi V, et al. "Diet and Alzheimer's disease risk factors or prevention: the current evidence." <i>Expert Review of Neurotherapeutics</i> 11.5 (2011): 677-708.	Not a systematic review
Sotiropoulos I, et al. "Stress and glucocorticoid footprints in the brain-the path from depression to Alzheimer's disease." <i>Neuroscience & Biobehavioral Reviews</i> 32.6 (2008): 1161-73.	Not a systematic review
Staessen JA, Wang JG and Thijs L. "What can be expected from optimal blood pressure	Not a systematic review

control?." <i>Journal of Hypertension - Supplement</i> 21.2 (2003): S3-9.	
Standridge JB, Zylstra RG and Adams SM. "Alcohol consumption: an overview of benefits and risks." <i>Southern Medical Journal</i> 97.7 (2004): 664-72.	AD was not an outcome/Risk estimates for AD not reported
Starkstein SE and Jorge R. "Dementia after traumatic brain injury." <i>International Psychogeriatrics</i> 17 Suppl 1.(2005): S93-107.	Not a systematic review
"Statins do not prevent dementia". <i>Nurses' Drug Alert</i> (2009): 35-6.	AD was not an outcome/Risk estimates for AD not reported
Strachan MW, et al. "The relationship between type 2 diabetes and dementia." <i>British Medical Bulletin</i> 88.1 (2008): 131-46.	Not a systematic review
Strydom A, et al. "Dementia in Older Adults With Intellectual Disabilities – Epidemiology, Presentation, and Diagnosis." <i>Journal of Policy and Practice in Intellectual Disabilities</i> 7.2 (2010): 96-110.	Does not examine etiological risk factors (incidence/prevalence study)
Sundermann EE, Maki PM and Bishop JR. "A review of estrogen receptor alpha gene (ESR1) polymorphisms, mood, and cognition." <i>Menopause</i> 17.4 (2010): 874-86.	Not a systematic review
Szatmari S and Bereczki D. "Procaine treatments for cognition and dementia." <i>Cochrane Database of Systematic Reviews</i> 4 (2008): CD005993.	AD was not an outcome/Risk estimates for AD not reported
Taner N.E.. "Genetics of Alzheimer's disease: Lessons learned in two decades". <i>Turk Noroloji Dergisi</i> 16.1 (2010): 1-11.	Not a systematic review
Teri L, McCurry SM and Logsdon RG. "Memory, thinking, and aging. What we know about what we know." <i>Western Journal of Medicine</i> 167.4 (1997): 269-75.	Not a systematic review
Thompson J. "Vitamins and minerals 4: overview of folate and the B vitamins." <i>Community Practitioner</i> 79.6 (2006): 197-8.	Not a systematic review
Timmer NM, et al. "Do amyloid -associated factors co-deposit with A in mouse models for Alzheimer's disease?." <i>Journal of Alzheimer's Disease</i> 22.2 (2010): 345-55.	Not a systematic review
Townsend KP and Pratico D. "Novel therapeutic opportunities for Alzheimer's disease: focus on nonsteroidal anti-inflammatory drugs." <i>FASEB Journal</i> 19.12 (2005): 1592-601.	Not a systematic review
Treves TA. "Epidemiology of Alzheimer's disease." <i>Psychiatric Clinics of North America</i> 14.2 (1991): 251-65.	Not a systematic review
Tsuno N and Homma A. "What is the association between depression and Alzheimer's disease?." <i>Expert Review of Neurotherapeutics</i> 9.11 (2009): 1667-76.	Not a systematic review
Tune LE. "Depression and Alzheimer's disease." <i>Depression & Anxiety</i> 8 Suppl 1.(1998): 91-5.	Not a systematic review
Tyas SL. Are tobacco and alcohol use related to Alzheimer's disease? Results from three Canadian data sets. Dissertation, University of Western Ontario, 1998. Web.	Not a systematic review
Uversky VN. "Intrinsic disorder in proteins associated with neurodegenerative diseases." <i>Frontiers in Bioscience</i> 14.(2009): 5188-238.	Not a systematic review
Valenzuela M and Sachdev P. "Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up." <i>American Journal of Geriatric Psychiatry</i> 17.3 (2009): 179-87.	AD was not an outcome/Risk estimates for AD not reported
Valenzuela MJ and Sachdev P. "Brain reserve and cognitive decline: a non-parametric systematic review." <i>Psychological Medicine</i> 36.8 (2006): 1065-73.	AD was not an outcome/Risk estimates for AD not reported
Valenzuela MJ and Sachdev P. "Brain reserve and dementia: a systematic review." <i>Psychological Medicine</i> 36.4 (2006): 441-54.	AD was not an outcome/Risk estimates for AD not reported

Van Den Heuvel C, Thornton E and Vink R. "Traumatic brain injury and Alzheimer's disease: a review." <i>Progress in Brain Research</i> 161.(2007): 303-16.	Not a systematic review
van Duijn CM, Stijnen T and Hofman A. "Risk factors for Alzheimer's disease: overview of the EURODEM collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group." <i>International Journal of Epidemiology</i> 20 Suppl 2.(1991): S4-12.	Not a systematic review
van Uffelen JG, et al. "The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review." <i>Clinical Journal of Sport Medicine</i> 18.6 (2008): 486-500.	AD was not an outcome/Risk estimates for AD not reported
Van Broeckhoven C., Nitsch R.M., et al, eds. "Genetics of late-onset neurodegenerative brain diseases". Conference: 10th International Conference AD/PD - Alzheimer's and Parkinson's Diseases: Advances, Concepts and New Challenges Barcelona Spain. Conference Start: 20110309 Conference End: 20110313 Conference Publication: (var.pagings) <i>Neurodegenerative Diseases</i> 8.(2011).	Not a systematic review
Van Dam F and Van Gool WA. "Hyperhomocysteinemia and Alzheimer's disease: A systematic review." <i>Archives of Gerontology & Geriatrics</i> 48.3 (2009): 425-30.	Not a systematic review
van Reekum R, Simard M and Cohen T. "The prediction and prevention of Alzheimer's disease--towards a research agenda." <i>Journal of Psychiatry & Neuroscience</i> 24.5 (1999): 413-30.	Not a systematic review
Varamini B. The role of long-chain polyunsaturated fatty acids and resveratrol in brain nutrition: From brain development to aging. Dissertation, Cornell University, 2010. Web.	Not a systematic review
Vasto S, et al. "Alzheimer's disease and genetics of inflammation: a pharmacogenomic vision." <i>Pharmacogenomics</i> 8.12 (2007): 1735-45.	Not a systematic review
Vearncombe KJ and Pachana NA. "Is cognitive functioning detrimentally affected after early, induced menopause?." <i>Menopause</i> 16.1 (2009): 188-98.	AD was not an outcome/Risk estimates for AD not reported
Verdoux H, Lagnaoui R and Begaud B. "Is benzodiazepine use a risk factor for cognitive decline and dementia? A literature review of epidemiological studies." <i>Psychological Medicine</i> 35.3 (2005): 307-15.	AD was not an outcome/Risk estimates for AD not reported
Verkaik R, et al. "The relationship between severity of Alzheimer's disease and prevalence of comorbid depressive symptoms and depression: a systematic review." <i>International Journal of Geriatric Psychiatry</i> 22.11 (2007): 1063-86.	Does not examine etiological risk factors
Vislocky LM and Fernandez ML. "Biomedical effects of grape products." <i>Nutrition Reviews</i> 68.11 (2010): 656-70.	AD was not an outcome/Risk estimates for AD not reported
von Gunten A, et al. "Neural substrates of cognitive and behavioral deficits in atypical Alzheimer's disease." <i>Brain Research Reviews</i> 51.2 (2006): 176-211.	Does not examine etiological risk factors
Wald DS, Kasturiratne A and Simmonds M. "Serum homocysteine and dementia: meta-analysis of eight cohort studies including 8669 participants." <i>Alzheimer's & Dementia</i> 7.4 (2011): 412-7.	AD was not an outcome/Risk estimates for AD not reported
Walter S., et al. "A genome-wide association study of aging". <i>Neurobiology of Aging</i> 32.11 (2011): 2109.e15-2109.e28.	Not a systematic review
Warren MP and Halpert S. "Hormone replacement therapy: controversies, pros and cons." <i>Best Practice & Research Clinical Endocrinology & Metabolism</i> 18.3 (2004): 317-32.	Not a systematic review
Warsch JR and Wright CB. "The aging mind: vascular health in normal cognitive aging." <i>Journal of the American Geriatrics Society</i> 58 Suppl 2.(2010): S319-24.	Not a systematic review
Wartenberg D. "EMFs: cutting through the controversy." <i>Public Health Reports</i> 111.3 (1996): 204-17.	Not a systematic review

Waters DD. "Exploring new indications for statins beyond atherosclerosis: Successes and setbacks." <i>Journal of Cardiology</i> 55.2 (2010): 155-62.	Not a systematic review
Watt NT, Whitehouse IJ and Hooper NM. "The role of zinc in Alzheimer's disease." <i>International journal of Alzheimer's disease</i> 2011.(2010): 971021.	Not a systematic review
Webster J, et al. "Whole genome association analysis shows that ACE is a risk factor for Alzheimer's disease and fails to replicate most candidates from Meta-analysis." <i>International Journal of Molecular Epidemiology and Genetics</i> 1.1 (2010): 19-30.	Not a systematic review
Weinmann S, et al. "Effects of Ginkgo biloba in dementia: systematic review and meta-analysis." <i>BMC Geriatrics</i> 10.(2010): 14.	Does not examine etiological risk factors
Weiss B. "Lead, manganese, and methylmercury as risk factors for neurobehavioral impairment in advanced age." <i>International journal of Alzheimer's disease</i> 2011.(2010): 607543.	Not a systematic review
Wells CE. "Chronic brain disease: an overview." <i>American Journal of Psychiatry</i> 135.1 (1978): 1-12.	Does not examine etiological risk factors
Weytingh MD, Bossuyt PM and van Crevel H. "Reversible dementia: more than 10% or less than 1%? A quantitative review." <i>Journal of Neurology</i> 242.7 (1995): 466-71.	AD was not an outcome/Risk estimates for AD not reported
Whitehouse CR, Boullata J and McCauley LA. "The potential toxicity of artificial sweeteners." <i>AAOHN Journal</i> 56.6 (2008): 251-9; quiz 260-1.	AD was not an outcome/Risk estimates for AD not reported
Winker MA. "Age versus ageing as a cause of dementia." <i>Lancet</i> 346.8988 (1995): 1486.	Not a systematic review
Wisdom NM. The effects of causative and susceptibility genes on the development of Alzheimer's disease: A meta-analytic approach. Dissertation, Oklahoma Christian University, 2005. Web.	AD was not an outcome/Risk estimates for AD not reported
Wollmer MA, et al. "Association study of cholesterol-related genes in Alzheimer's disease." <i>Neurogenetics</i> 8.3 (2007): 179-88.	Not a systematic review
Wolozin B, et al. "Re-assessing the relationship between cholesterol, statins and Alzheimer's disease." <i>Acta Neurologica Scandinavica. Supplementum</i> 185.(2006): 63-70.	Not a systematic review
Wood WG and Igbavboa U. "Cholesterol trafficking and amyloid beta peptides." <i>Pharmacopsychiatry</i> 36 Suppl 2.(2003): S144-8.	Not a systematic review
Wostyn P, et al. "Increased Cerebrospinal Fluid Production as a Possible Mechanism Underlying Caffeine's Protective Effect against Alzheimer's Disease." <i>International journal of Alzheimer's disease</i> 2011.(2011): 617420.	Not a systematic review
Wynn M and Wynn A. "The danger of B12 deficiency in the elderly." <i>Nutrition & Health</i> 12.4 (1998): 215-26.	Not a systematic review
Yesufu A, Bandelow S and Hogervorst E. "Meta-analyses of the effect of hormone treatment on cognitive function in postmenopausal women." <i>Women's health</i> 3.2 (2007): 173-94.	Not a systematic review
Yi ES, Abraham IL and Holroyd S. "Alzheimer's disease and nursing. New scientific and clinical insights." <i>Nursing Clinics of North America</i> 29.1 (1994): 85-99.	Not a systematic review
Yu JT, Chang RC and Tan L. "Calcium dysregulation in Alzheimer's disease: from mechanisms to therapeutic opportunities." <i>Progress in Neurobiology</i> 89.3 (2009): 240-55.	Not a systematic review
Zawia NH and Basha MR. "Environmental risk factors and the developmental basis for Alzheimer's disease." <i>Reviews in the Neurosciences</i> 16.4 (2005): 325-37.	Not a systematic review
Zec RF and Trivedi MA. "Hormonal replacement therapy and cognition in postmenopausal women." <i>JAMA</i> 285.23 (2001): 2974-5.	AD was not an outcome/Risk estimates for AD not reported

Zhu BT. "Catechol-O-Methyltransferase (COMT)-mediated methylation metabolism of endogenous bioactive catechols and modulation by endobiotics and xenobiotics: importance in pathophysiology and pathogenesis." <i>Current Drug Metabolism</i> 3.3 (2002): 321-49.	Does not examine etiological risk factors
Zigman W, et al. "The epidemiology of Alzheimer disease in intellectual disability: results and recommendations from an international conference." <i>Journal of Intellectual Disability Research</i> 41 (Pt 1).(1997): 76-80.	Not a systematic review
Zoccolella S, et al. "Hyperhomocysteinemia in movement disorders: Current evidence and hypotheses." <i>Current Vascular Pharmacology</i> 4.3 (2006): 237-43.	AD was not an outcome/Risk estimates for AD not reported

APPENDIX A-4: Excluded Studies (AMSTAR score $\leq$ 3) (n=39)

Study	AMSTAR Quality Score
Bang OY, et al. "Important link between dementia subtype and apolipoprotein E: A meta-analysis." <i>Yonsei Medical Journal</i> 44.3 (2003): 401-413.	2
Barnes DR, et al. "The projected effect of risk factor reduction on Alzheimer's disease prevalence." <i>Lancet Neurology</i> 10 (2011): 819-828.	3
Bates MN. "Mercury amalgam dental fillings: An epidemiological assessment." <i>International Journal of Hygiene and Environmental Health</i> 209 (2006): 309-316.	2
Beri A, et al. "Non-Atheroprotective Effects of Statins." <i>American Journal of Cardiovascular Drugs</i> 9.6 (2009): 361- 370.	3
Brinker K, et al. "Serum Lipids and Statin Therapy in Relation to Alzheimer's Disease: Exploring the Relationship Between Elevated Serum Cholesterol Levels and Alzheimer's Disease Dementia." Diss. Cornell University, 2011, Web.	2
Bruscoli M, et al. "Is MCI really just early dementia? A systematic review of conversion studies." <i>International Psychogeriatrics</i> 16.2 (2004): 129-140.	3
Chang CL, et al. "Obesity and Alzheimer's Disease." <i>Hong Kong Journal of Psychiatry</i> 18 (2008): 28-35.	3
Conti A, et al. The potential role of leisure in the prevention of dementia. <i>Annual in Therapeutic Recreation</i> (2009).	3
Coppus AMW, et al. "The impact of apolipoprotein E on dementia in persons with Down's syndrome." <i>Neurobiology of Aging</i> 29 (2008): 828-835.	3
Del Bo RD, et al. "Is M129V of PRNP gene associated with Alzheimer's disease? A case-control study and a meta-analysis." <i>Neurobiology of Aging</i> 27 (2006): 770e1-770.e5.	2
Desilets A, et al. "The Role of Statins in the Prevention and Treatment of Alzheimer's Disease." <i>Journal of Pharmacy Technology</i> 26 (2010): 276 – 284.	3
Ferreira PC, et al. "Aluminum as a risk factor for Alzheimer's disease." <i>Rev Latino-am Enfermagem</i> 16.1 (2008): 151-157.	1
Fotuhi M, et al. "Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: a complex association." <i>Nature Clinical Practice</i> 5.3 (2009): 140 – 152.	3
Fratiglioni L et al. "An active and socially integrated lifestyle in late life might protect against dementia." <i>Lancet Neurology</i> 3 (2004): 343-53.	3
Hurley BF, et al. "Strength Training as a Countermeasure to Aging Muscle and Chronic Disease." <i>Sports Medicine</i> 41.4 (2011): 289-306.	1
Jorm A, et al. "History of depression as a risk factor for dementia: an updated review." <i>Australian and New Zealand Journal of Psychiatry</i> 35 (2001): 776-781.	2
Keage HAD, et al. "Population studies of sporadic cerebral amyloid angiopathy and dementia: a systematic review." <i>BMC Neurology</i> 9.3 (2009): 1-8.	2
Kheifets L, et al. "Future needs of occupational epidemiology of extremely low frequency electric and magnetic fields: review and recommendations." <i>Occupational and Environmental Medicine</i> 66 (2009): 72-80.	2
Kopf D, et al. "Risk of Incident Alzheimer's Disease in Diabetic Patients: A Systematic Review of Prospective Trials." <i>Journal of Alzheimer's Disease</i> 16 (2009): 677 – 685.	2
Kuo HK, et al. "The Role of Homocysteine in Multisystem Age-Related Problems: A Systematic Review." <i>Journal of Gerontology</i> 60A.9 (2005): 1190-1201.	2
LaRoia H, et al. "Association between Essential Tremor and Other Neurodegenerative Diseases: What is the Epidemiological Evidence?" <i>Neuroepidemiology</i> 37 (2011): 1-10.	2
Loef M, et al. "Copper and iron in Alzheimer's disease: a systematic review and its dietary implications." <i>British Journal of Nutrition</i> (2011).	3

Loef M, et al. "Lead (Pb) and the Risk of Alzheimer's disease or cognitive decline: A systematic review." <i>Toxin Reviews</i> 30.4 (2011): 103-114.	2
Low LF, et al., "Will testing for apolipoprotein E assist in tailoring dementia risk reduction? A review." <i>Neuroscience and Behavioural Reviews</i> 34 (2010): 408-437.	3
Miller J, et al. "The Role of Cholesterol and Statins in Alzheimer's Disease." <i>Annals of Pharmacotherapy</i> 38 (2004): 91-98.	2
Mitchell AJ, et al. "Temporal trends in the long term risk of progression of mild cognitive impairment: a pooled analysis." <i>Journal of Neurology, Neurosurgery and Psychiatry</i> 79 (2008): 1386-1391.	3
Patatanian E, et al. "The Future of Statins: Alzheimer's Disease?" <i>The Consultant Pharmacist</i> 20.8 (2005): 663 – 673.	3
Penrose FK. "Can Exercise Affect Cognitive Functioning in Alzheimer's Disease? A Review of the Literature." <i>Activities, Adaptation & Aging</i> 29.4 (2005): 15-40.	2
Pham DQ, et al. "Vitamin E Supplementation in Alzheimer's Disease, Parkinson's Disease, Tardive Dyskinesia, and Cataract: Part 2." <i>Annals of Pharmacotherapy</i> 39 (2005): 2065-72.	2
Pitner JK. "Obesity in the Elderly." <i>The Consultant Pharmacist</i> 20.6 (2005): 498-513.	1
Purnell C, et al. "Cardiovascular Risk Factors and Incident Alzheimer's Disease: A Systematic Review of the Literature." <i>Alzheimer Disease and Associated Disorders</i> 23.1 (2009): 1-10.	2
Reutens S, et al. "Homocysteine in neuropsychiatric disorders of the elderly." <i>International Journal of Geriatric Psychiatry</i> 17.9 (2002): 859-64.	2
Reynolds CA, et al. "Sequence variation in SORL1 and dementia risk in Swedes." <i>Neurogenetics</i> 11 (2010): 139-142.	1
Roman B, et al. "Effectiveness of the Mediterranean diet in the elderly." <i>Clinical Interventions in Aging</i> 3.1 (2008): 97-109.	2
Rubinsztein DC, et al. "Apolipoprotein E Genetic Variation and Alzheimer's Disease: A Meta-Anaysis." <i>Dementia and Geriatric Cognitive Disorders</i> 10 (1999): 199-209.	3
Shadlen MF, et al. "The epidemiology of Alzheimer's disease and vascular dementia in Japanese and African-American populations: the search for etiological clues." <i>Neurobiology of Aging</i> 21 (2000): 171-181.	2
Standridge JB, et al. "Pharmacotherapeutic Approaches to the Prevention of Alzheimer's Disease." <i>The American Journal of Geriatric Pharmacotherapy</i> 2 (2004): 119-132.	3
The ESHRE Capri Workshop Group. "Perimenopausal risk factors and future health." <i>Human Reproduction Update</i> 17.5 (2011): 706 – 717.	1
van Gool et al. "A Case-Control Study of Apolipoprotein E Genotypes in Alzheimer's Disease Associated with Down's Syndrome." <i>Annals of Neurology</i> 38.2 (1995): 225-230.	1

APPENDIX A-5: Included Studies (n=27)

Almeida OP, et al. "Smoking as a risk factor for Alzheimer's disease: contrasting evidence from a systematic review of case-control and cohort studies." <i>Addiction</i> 97.1 (2002): 15-28.	Peters R, et al. "Alcohol, dementia and cognitive decline in the elderly: a systematic review." <i>Age & Ageing</i> 37.5 (2008): 505-12.
Anstey KJ, et al. "Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies." <i>American Journal of Geriatric Psychiatry</i> 17.7 (2009): 542 – 555.	Peters R, et al. "Smoking, dementia and cognitive decline in the elderly, a systematic review." <i>BMC Geriatrics</i> 8:36 (2008).
Anstey KJ, et al. "Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies." <i>American Journal of Epidemiology</i> 166.4 (2007): 367-78.	Podewils LJ. Physical activity and dementia risk: A prospective study. Dissertation, Johns Hopkins University, 2003. Web.
Barranco Quintana JL, et al. "Alzheimer's disease and coffee: a quantitative review." <i>Neurological Research</i> 29.1 (2007): 91-5.	Raman G, et al. "Heterogeneity and lack of good quality studies limit association between folate, vitamins B-6 and B-12, and cognitive function." <i>Journal of Nutrition</i> 137 (2007): 1789-94.
Cataldo JK, et al. "Cigarette smoking is a risk factor for Alzheimer's disease: an analysis controlling for tobacco industry affiliation." <i>Journal of Alzheimer's disease</i> 19 (2010): 465 - 480.	Rolland Y., Abellan van Kan G. and Vellas B. "Physical activity and Alzheimer's disease: from prevention to therapeutic perspectives". <i>Journal of the American Medical Directors Association</i> 9.6 (2008): 390-405.
Caamano-Isorna F, et al. "Education and dementia: a meta-analytic study." <i>Neuroepidemiology</i> 26 (2006): 226-232.	Santos C, et al. "Caffeine intake and dementia: systematic review and meta-analysis." <i>Journal of Alzheimer's Disease</i> 20 Suppl 1.(2010): S187-204.
Crichton GE, et al. "Review of dairy consumption and cognitive performance in adults: findings and methodological issues." <i>Dementia & Geriatric Cognitive Disorders</i> 30.4 (2010): 352-61.	Sofi F, et al. "Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis." <i>American Journal of Clinical Nutrition</i> 92.5 (2010): 1189-96.
Dangour AD, et al. "B-Vitamins and fatty acids in the prevention and treatment of Alzheimer's disease and dementia: a systematic review." <i>Journal of Alzheimer's Disease</i> 22 (2010): 205-224.	Sofi F, et al. "Adherence to Mediterranean diet and health status: meta-analysis." <i>BMJ</i> 337.(2008): a1344.
Graves AB, et al. "Alcohol and tobacco consumption as risk factors for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group." <i>International Journal of Epidemiology</i> 20 Suppl 2.(1991): S48-57.	Stern C, et al. "Cognitive leisure activities and their role in preventing dementia: a systematic review." <i>International Journal of Evidence Based Healthcare</i> 8 (2010): 2-17."
Hamer M and Chida Y. "Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence." <i>Psychological Medicine</i> 39.1 (2009): 3-11.	Stern C and Konno R. "Physical leisure activities and their role in preventing dementia: a systematic review." <i>International Journal of Evidence-Based Healthcare</i> 7.4 (2009): 270-82.
Issa AM, et al. "The efficacy of omega-3 fatty acids on	Williams JW, et al. "Preventing Alzheimer's Disease

cognitive function in aging and dementia: a systematic review." <i>Dementia & Geriatric Cognitive Disorders</i> 21.2 (2006): 88-96.	and Cognitive Decline." Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.
Lee Y, et al. "Systematic review of health behaviour risks and cognitive health in older adults." <i>International Psychogeriatrics</i> 22.2 (2010): 174-187.	Weih M, et al. "Non-pharmacologic prevention of Alzheimer's disease: nutritional and life-style risk factors." <i>Journal of Neural Transmission</i> 114 (2007): 1187-1197.
Lim WS, et al. "Omega 3 fatty acid for the prevention of dementia." <i>Cochrane Database of Systematic Reviews</i> 1 (2006): CD005379.	Weih M., et al. "Physical activity and Alzheimer's disease: A meta-analysis of cohort studies". <i>GeroPsych: The Journal of Gerontopsychology and Geriatric Psychiatry</i> 23.1 (2010): 17-20.
Patterson C, et al. "General risk factors for dementia: A systematic evidence review." <i>Alzheimer's and Dementia</i> 3 (2007): 341-7.	

APPENDIX A-6: AMSTAR Scoring by Item for Included and Excluded studies

	AMSTAR Criteria (a total of 1 point can be assigned per criterion)											
Study	1	2	3	4	5	6	7	8	9	10	11	Total (categorization of quality)
SMOKING												
Graves, AB. “Alcohol and tobacco consumption as risk factors for Alzheimer’s disease: a collaborative re-analysis of case-control studies.” International Journal of Epidemiology 20.2 Suppl 2 (1991): S48-S57.	1	0	0	0	0	1	0	1	1	0	0	4 (Moderate)
Almeida OP, et al. "Smoking as a risk factor for Alzheimer's disease: contrasting evidence from a systematic review of case-control and cohort studies." Addiction 97.1 (2002): 15-28.	1	0	0	0	0	1	1	1	0	0	0	4 (Moderate)
Anstey KJ, et al. "Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies." American Journal of Epidemiology 166.4 (2007): 367-78.	1	0	0	0	0	1	0	1	1	0	0	4 (Moderate)
Weih M, et al. “Non-pharmacologic prevention of Alzheimer’s disease: nutritional and life-style risk factors.” Journal of Neural Transmission 114 (2007): 1187-1197.	1	0	1	1	0	1	1	1	N/A	0	0	6 (Moderate)
Patterson C, et al. “General risk factors for dementia: A systematic evidence review.” Alzheimer’s and Dementia 3 (2007): 341-7.	1	0	1	0	0	0	1	1	N/A	0	0	4 (Moderate)
Peters R, et al. “Smoking, dementia and cognitive decline in	1	0	0	0	0	1	1	1	1	1	0	6 (Moderate)

the elderly, a systematic review." BMC Geriatrics 8:36 (2008).												
Purnell C, et al. "Cardiovascular Risk Factors and Incident Alzheimer's Disease: A Systematic Review of the Literature." Alzheimer Disease and Associated Disorders 23.1 (2009): 1-10.	1	0	0	0	0	0	0	1	N/A	0	0	2 (Low)
Cataldo JK, et al. "Cigarette Smoking is a Risk Factor for Alzheimer's Disease: An Analysis Controlling for Tobacco Industry Affiliation." Journal of Alzheimer's disease 19 (2010): 465 - 480.	1	0	0	0	0	1	1	1	1	1	1	7 (Moderate)
Lee Y, et al. "Systematic review of health behaviour risks and cognitive health in older adults." International Psychogeriatrics 22.2 (2010): 174-187.	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)
Williams JW, et al. "Preventing Alzheimer's Disease and Cognitive Decline." Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHS 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)
The ESHRE Capri Workshop Group. "Perimenopausal risk factors and future health." Human Reproduction Update 17.5 (2011): 706 – 717.	1	0	0	0	0	0	0	0	N/A	0	0	1 (Low)
Barnes DR, et al. "The projected effect of risk factor reduction on Alzheimer's disease prevalence." Lancet Neurology 10 (2011): 819-828.	1	0	0	0	0	0	0	1	N/A	0	0	2 (Low)
ALCOHOL												
Graves, AB. "Alcohol and tobacco consumption as risk factors for	1	0	0	0	0	1	0	1	1	0	0	4 (Moderate)

Alzheimer's disease: a collaborative re-analysis of case-control studies. International Journal of Epidemiology 20.2 Suppl 2 (1991): S48-S57.												
Standridge JB, et al. "Pharmacotherapeutic Approaches to the Prevention of Alzheimer's Disease." The American Journal of Geriatric Pharmacotherapy 2 (2004): 119-132.	1	0	0	0	0	0	1	1	N/A	0	0	3 (Low)
Patterson C, et al. "General risk factors for dementia: A systematic evidence review." Alzheimer's and Dementia 3 (2007): 341-7.	1	0	1	0	0	0	1	1	N/A	0	0	4 (Moderate)
Weih M, et al. "Non-pharmacologic prevention of Alzheimer's disease: nutritional and life-style risk factors." Journal of Neural Transmission 114 (2007): 1187-1197.	1	0	1	1	0	1	1	1	N/A	0	0	6 (Moderate)
Peters R, et al. "Alcohol, dementia and cognitive decline in the elderly: a systematic review." Age & Ageing 37.5 (2008): 505-12.	1	1	0	0	0	0	1	1	1	1	0	6 (Moderate)
Anstey KJ, et al. "Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies." American Journal of Geriatric Psychiatry 17.7 (2009): 542 – 555.	1	0	0	0	0	1	0	1	1	0	0	4 (Moderate)
Purnell C, et al. "Cardiovascular Risk Factors and Incident Alzheimer's Disease: A Systematic Review of the Literature." Alzheimer Disease and Associated Disorders 23.1 (2009): 1-10.	1	0	0	0	0	0	0	1	N/A	0	0	2 (Low)
Lee Y, et al. "Systematic review of health behaviour risks and	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)

cognitive health in older adults.” International Psychogeriatrics 22.2 (2010): 174-187.												
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)
The ESHRE Capri Workshop Group. “Perimenopausal risk factors and future health.” Human Reproduction Update 17.5 (2011): 706 – 717.	1	0	0	0	0	0	0	0	N/A	0	0	1 (Low)
MEDITERRANEAN DIET												
Weih M, et al. “Non-pharmacologic prevention of Alzheimer’s disease: nutritional and life-style risk factors.” Journal of Neural Transmission 114 (2007): 1187-1197.	1	0	1	1	0	1	1	1	N/A	0	0	6 (Moderate)
Roman B, et al. “Effectiveness of the Mediterranean diet in the elderly.” Clinical Interventions in Aging 3.1 (2008): 97-109.	1	0	0	0	0	1	0	0	N/A	0	0	2 (Low)
Sofi F, et al. “Adherence to Mediterranean diet and health status: meta-analysis.” BMJ 337.(2008): a1344.	1	0	0	0	0	1	1	1	1	1	0	6 (Moderate)
Sofi F, et al. “Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis.” American Journal of Clinical Nutrition 92.5 (2010): 1189-96.	1	1	1	1	0	1	1	1	1	1	0	9 (High)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)

Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHS 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.												
The ESHRE Capri Workshop Group. “Perimenopausal risk factors and future health.” Human Reproduction Update 17.5 (2011): 706 – 717.	1	0	0	0	0	0	0	0	N/A	0	0	1 (Low)
CAFFEINE/COFFEE/TEA												
Barranco Quintana JL, et al. “Alzheimer's disease and coffee: a quantitative review.” Neurological Research 29.1 (2007): 91-5.	1	0	1	0	0	0	0	1	1	0	0	4 (Moderate)
Santos C, et al. “Caffeine intake and dementia: systematic review and meta-analysis.” Journal of Alzheimer's Disease 20 Suppl 1.(2010): S187-204.	1	1	0	0	0	1	0	1	1	1	0	6 (Moderate)
Lee Y, et al. “Systematic review of health behaviour risks and cognitive health in older adults.” International Psychogeriatrics 22.2 (2010): 174-187.	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)
POLYUNSATURATED FATTY ACIDS/OMEGA-3 FATTY ACIDS/ OMEGA-6 FATTY ACIDS												
Standridge JB, et al. “Pharmacotherapeutic Approaches to the Prevention of Alzheimer's Disease.” The American Journal of Geriatric Pharmacotherapy 2 (2004): 119-132.	1	0	0	0	0	0	1	1	N/A	0	0	3 (Low)
Issa AM, et al. “The efficacy of omega-3 fatty acids on cognitive function in aging and dementia: a systematic review.” Dementia & Geriatric Cognitive Disorders 21.2 (2006): 88-96.	1	1	0	1	0	1	1	1	N/A	0	1	7 (Moderate)

Weih M, et al. “Non-pharmacologic prevention of Alzheimer’s disease: nutritional and life-style risk factors.” Journal of Neural Transmission 114 (2007): 1187-1197.	1	0	1	1	0	1	1	1	N/A	0	0	6 (Moderate)
Patterson C, et al. “General risk factors for dementia: A systematic evidence review.” Alzheimer’s and Dementia 3 (2007): 341-7.	1	0	1	0	0	0	1	1	N/A	0	0	4 (Moderate)
Lim WS, et al. “Omega 3 fatty acid for the prevention of dementia.” Cochrane Database of Systematic Reviews 1 (2009): CD005379.	1	1	1	1	1	1	1	1	1	1	0	10 (High)
Fotuhi M, et al. “Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: a complex association.” Nature Clinical Practice 5.3 (2009): 140 – 152.	1	0	0	0	0	1	0	1	N/A	0	0	3 (Low)
Dangour AD, et al. “B-Vitamins and Fatty Acids in the Prevention and Treatment of Alzheimer’s Disease and Dementia: A Systematic Review.” Journal of Alzheimer’s Disease 22 (2010): 205-224.	1	0	0	0	1	1	1	1	N/A	0	0	5 (Moderate)
Lee Y, et al. “Systematic review of health behaviour risks and cognitive health in older adults.” International Psychogeriatrics 22.2 (2010): 174-187.	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)

Quality. April 2010.												
CALORIC INTAKE												
Weih M, et al. “Non-pharmacologic prevention of Alzheimer’s disease: nutritional and life-style risk factors.” Journal of Neural Transmission 114 (2007): 1187-1197.	1	0	1	1	0	1	1	1	N/A	0	0	6 (Moderate)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)
FAT INTAKE/SATURATED FATTY ACIDS												
Weih M, et al. “Non-pharmacologic prevention of Alzheimer’s disease: nutritional and life-style risk factors.” Journal of Neural Transmission 114 (2007): 1187-1197.	1	0	1	1	0	1	1	1	N/A	0	0	6 (Moderate)
Crichton GE, et al. “Review of Dairy Consumption and Cognitive Performance in Adults: Findings and Methodological Issues.” Dementia and Geriatric Cognitive Disorders 30 (2010): 352-361.	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)
Lee Y, et al. “Systematic review of health behaviour risks and cognitive health in older adults.” International Psychogeriatrics 22.2 (2010): 174-187.	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0.	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)

193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.												
MULTIVITAMINS												
Standridge JB, et al. “Pharmacotherapeutic Approaches to the Prevention of Alzheimer’s Disease.” The American Journal of Geriatric Pharmacotherapy 2 (2004): 119-132.	1	0	0	0	0	0	1	1	N/A	0	0	3 (Low)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)
VITAMIN B12												
Standridge JB, et al. “Pharmacotherapeutic Approaches to the Prevention of Alzheimer’s Disease.” The American Journal of Geriatric Pharmacotherapy 2 (2004): 119-132.	1	0	0	0	0	0	1	1	N/A	0	0	3 (Low)
Raman G, et al. “Heterogeneity and lack of good quality studies limit association between folate, vitamins B-6 and B-12, and cognitive function.” Journal of Nutrition 137 (2007): 1789-94.	1	0	0	1	0	1	1	1	N/A	0	0	5 (Moderate)
Purnell C, et al. “Cardiovascular Risk Factors and Incident Alzheimer’s Disease: A Systematic Review of the	1	0	0	0	0	0	0	1	N/A	0	0	2 (Low)

Literature.” Alzheimer Disease and Associated Disorders 23.1 (2009): 1-10.												
Dangour AD, et al. “B-Vitamins and Fatty Acids in the Prevention and Treatment of Alzheimer’s Disease and Dementia: A Systematic Review.” Journal of Alzheimer’s Disease 22 (2010): 205-224.	1	0	0	0	1	1	1	1	N/A	0	0	5 (Moderate)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)
Lee Y, et al. “Systematic review of health behaviour risks and cognitive health in older adults.” International Psychogeriatrics 22.2 (2010): 174-187.	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)
VITAMIN B-3/NIACIN												
Standridge JB, et al. “Pharmacotherapeutic Approaches to the Prevention of Alzheimer’s Disease.” The American Journal of Geriatric Pharmacotherapy 2 (2004): 119-132.	1	0	0	0	0	0	1	1	N/A	0	0	3 (Low)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)

Quality. April 2010.												
Lee Y, et al. “Systematic review of health behaviour risks and cognitive health in older adults.” International Psychogeriatrics 22.2 (2010): 174-187.	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)
VITAMIN B6												
Standridge JB, et al. “Pharmacotherapeutic Approaches to the Prevention of Alzheimer’s Disease.” The American Journal of Geriatric Pharmacotherapy 2 (2004): 119-132.	1	0	0	0	0	0	1	1	N/A	0	0	3 (Low)
Raman G, et al. “Heterogeneity and lack of good quality studies limit association between folate, vitamins B-6 and B-12, and cognitive function.” Journal of Nutrition 137 (2007): 1789-94.	1	0	0	1	0	1	1	1	N/A	0	0	5 (Moderate)
Purnell C, et al. “Cardiovascular Risk Factors and Incident Alzheimer’s Disease: A Systematic Review of the Literature.” Alzheimer Disease and Associated Disorders 23.1 (2009): 1-10.	1	0	0	0	0	0	0	1	N/A	0	0	2 (Low)
Dangour AD, et al. “B-Vitamins and Fatty Acids in the Prevention and Treatment of Alzheimer’s Disease and Dementia: A Systematic Review.” Journal of Alzheimer’s Disease 22 (2010): 205-224.	1	0	0	0	1	1	1	1	N/A	0	0	5 (Moderate)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)

Quality. April 2010.												
VITAMIN C												
Standridge JB, et al. “Pharmacotherapeutic Approaches to the Prevention of Alzheimer’s Disease.” The American Journal of Geriatric Pharmacotherapy 2 (2004): 119-132.	1	0	0	0	0	0	1	1	N/A	0	0	3 (Low)
Weih M, et al. “Non-pharmacologic prevention of Alzheimer’s disease: nutritional and life-style risk factors.” Journal of Neural Transmission 114 (2007): 1187-1197.	1	0	1	1	0	1	1	1	N/A	0	0	6 (Moderate)
Lee Y, et al. “Systematic review of health behaviour risks and cognitive health in older adults.” International Psychogeriatrics 22.2 (2010): 174-187.	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)
VITAMIN E												
Standridge JB, et al. “Pharmacotherapeutic Approaches to the Prevention of Alzheimer’s Disease.” The American Journal of Geriatric Pharmacotherapy 2 (2004): 119-132.	1	0	0	0	0	0	1	1	N/A	0	0	3 (Low)
Pham DQ, et al. “Vitamin E Supplementation in Alzheimer’s Disease, Parkinson’s Disease, Tardive Dyskinesia, and Cataract:	1	0	0	0	0	0	0	1	N/A	0	0	2 (Low)

Part 2.” Annals of Pharmacotherapy 39 (2005): 2065-72.												
Weih M, et al. “Non-pharmacologic prevention of Alzheimer’s disease: nutritional and life-style risk factors.” Journal of Neural Transmission 114 (2007): 1187-1197.	1	0	1	1	0	1	1	1	N/A	0	0	6 (Moderate)
Patterson C, et al. “General risk factors for dementia: A systematic evidence review.” Alzheimer’s and Dementia 3 (2007): 341-7.	1	0	1	0	0	0	1	1	N/A	0	0	4 (Moderate)
Lee Y, et al. “Systematic review of health behaviour risks and cognitive health in older adults.” International Psychogeriatrics 22.2 (2010): 174-187.	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)
FOLIC ACID/FOLATE												
Standridge JB, et al. “Pharmacotherapeutic Approaches to the Prevention of Alzheimer’s Disease.” The American Journal of Geriatric Pharmacotherapy 2 (2004): 119-132.	1	0	0	0	0	0	1	1	N/A	0	0	3 (Low)
Raman G, et al. “Heterogeneity and lack of good quality studies limit association between folate, vitamins B-6 and B-12, and cognitive function.” Journal of Nutrition 137 (2007): 1789-94.	1	0	0	1	0	1	1	1	N/A	0	0	5 (Moderate)

Weih M, et al. “Non-pharmacologic prevention of Alzheimer’s disease: nutritional and life-style risk factors.” Journal of Neural Transmission 114 (2007): 1187-1197.	1	0	1	1	0	1	1	1	N/A	0	0	6 (Moderate)
Dangour AD, et al. “B-Vitamins and Fatty Acids in the Prevention and Treatment of Alzheimer’s Disease and Dementia: A Systematic Review.” Journal of Alzheimer’s Disease 22 (2010): 205-224.	1	0	0	0	1	1	1	1	N/A	0	0	5 (Moderate)
Lee Y, et al. “Systematic review of health behaviour risks and cognitive health in older adults.” International Psychogeriatrics 22.2 (2010): 174-187.	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)
FLAVONOIDS												
Standridge JB, et al. “Pharmacotherapeutic Approaches to the Prevention of Alzheimer’s Disease.” The American Journal of Geriatric Pharmacotherapy 2 (2004): 119-132.	1	0	0	0	0	0	1	1	N/A	0	0	3 (Low)
Lee Y, et al. “Systematic review of health behaviour risks and cognitive health in older adults.” International Psychogeriatrics 22.2 (2010): 174-187.	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)
Williams JW, et al. “Preventing	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)

Alzheimer's Disease and Cognitive Decline." Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.												
FRUIT AND VEGETABLE CONSUMPTION												
Lee Y, et al. "Systematic review of health behaviour risks and cognitive health in older adults." International Psychogeriatrics 22.2 (2010): 174-187.	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)
Williams JW, et al. "Preventing Alzheimer's Disease and Cognitive Decline." Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)
BETA-CAROTENE												
Standridge JB, et al. "Pharmacotherapeutic Approaches to the Prevention of Alzheimer's Disease." The American Journal of Geriatric Pharmacotherapy 2 (2004): 119-132.	1	0	0	0	0	0	1	1	N/A	0	0	3 (Low)
Weih M, et al. "Non-pharmacologic prevention of Alzheimer's disease: nutritional and life-style risk factors." Journal of Neural Transmission 114 (2007): 1187-1197.	1	0	1	1	0	1	1	1	N/A	0	0	6 (Moderate)
Lee Y, et al. "Systematic review of health behaviour risks and	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)

cognitive health in older adults.” International Psychogeriatrics 22.2 (2010): 174-187.												
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)
COGNITIVE LEISURE ACTIVITIES												
Weih M, et al. “Non-pharmacologic prevention of Alzheimer’s disease: nutritional and life-style risk factors.” Journal of Neural Transmission 114 (2007): 1187-1197.	1	0	1	1	0	1	1	1	N/A	0	0	6 (Moderate)
Stern C, et al. “Cognitive leisure activities and their role in preventing dementia: a systematic review.” International Journal of Evidence Based Healthcare 8 (2010): 2-17.” br 150	1	0	0	1	0	1	1	1	N/A	0	0	5 (Moderate)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)
Fratiglioni L et al. “An active and socially integrated lifestyle in late life might protect against dementia.” Lancet Neurology	1	0	0	0	0	1	0	1	N/A	0	0	3 (Low)

3(2004): 343-53.												
Barnes DR, et al. “The projected effect of risk factor reduction on Alzheimer’s disease prevalence.” Lancet Neurology 10 (2011): 819-828.	1	0	0	0	0	0	0	1	N/A	0	0	2 (Low)
SOCIAL ENGAGEMENT												
Fratiglioni L et al. “An active and socially integrated lifestyle in late life might protect against dementia.” Lancet Neurology 3 (2004): 343-53.	1	0	0	0	0	1	0	1	N/A	0	0	3 (Low)
Weih M, et al. “Non-pharmacologic prevention of Alzheimer’s disease: nutritional and life-style risk factors.” Journal of Neural Transmission 114 (2007): 1187-1197.	1	0	1	1	0	1	1	1	N/A	0	0	6 (Moderate)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)
EDUCATION												
Caamano-Isorna F, et al. “Education and Dementia : A Meta-Analytic Study.” Neuroepidemiology 26 (2006): 226-232.	1	0	0	0	0	1	0	1	1	1	0	5 (Moderate)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)

No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.												
Patterson C, et al. “General risk factors for dementia: A systematic evidence review.” Alzheimer’s and Dementia 3 (2007): 341-7.	1	0	1	0	0	0	1	1	N/A	0	0	4 (Moderate)
Barnes DR, et al. “The projected effect of risk factor reduction on Alzheimer’s disease prevalence.” Lancet Neurology 10 (2011): 819-828.	1	0	0	0	0	0	0	1	N/A	0	0	2 (Low)
PHYSICAL ACTIVITY												
Podewils LJ. “Physical activity and dementia risk: a systematic review.” Dissertation, Johns Hopkins University, 2003. Web.	1	1	0	0	0	1	1	1	1	1	0	7 (Moderate)
Fratiglioni L et al. “An active and socially integrated lifestyle in late life might protect against dementia.” Lancet Neurology 3 (2004): 343-53.	1	0	0	0	0	1	0	1	N/A	0	0	3 (Low)
Penrose FK. “Can Exercise Affect Cognitive Functioning in Alzheimer’s Disease? A Review of the Literature.” Activities, Adaptation & Aging 29.4 (2005): 15-40.	1	0	0	0	0	0	0	1	N/A	0	0	2 (Low)
Weih M, et al. “Non-pharmacologic prevention of Alzheimer’s disease: nutritional and life-style risk factors.” Journal of Neural Transmission 114 (2007): 1187-1197.	1	0	1	1	0	1	1	1	N/A	0	0	6 (Moderate)
Patterson C, et al. “General risk factors for dementia: A systematic evidence review.” Alzheimer’s and Dementia 3 (2007): 341-7.	1	0	1	0	0	0	1	1	N/A	0	0	4 (Moderate)
Rolland Y, et al. “Physical activity and Alzheimer’s disease: from prevention to therapeutic perspectives.” Journal of the American Medical Directors	1	0	0	1	0	1	0	1	N/A	0	0	4 (Moderate)

Association 9 (2008): 390-405.												
Purnell C, et al. “Cardiovascular Risk Factors and Incident Alzheimer’s Disease: A Systematic Review of the Literature.” Alzheimer Disease and Associated Disorders 23.1 (2009): 1-10.	1	0	0	0	0	0	0	1	N/A	0	0	2 (Low)
Hamer M and Y Chida. “Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence.” Psychological Medicine 39 (2009): 3-11.	1	0	0	0	0	1	1	1	1	1	0	6 (Moderate)
Stern C, et al. “Physical leisure activities and their role in preventing dementia: a systematic review.” International Journal of Evidence Based Healthcare 7 (2009): 270-82.	1	0	1	1	0	1	1	1	N/A	0	0	6 (Moderate)
Lee Y, et al. “Systematic review of health behaviour risks and cognitive health in older adults.” International Psychogeriatrics 22.2 (2010): 174-187.	1	0	0	0	0	1	1	1	N/A	0	0	4 (Moderate)
Williams JW, et al. “Preventing Alzheimer’s Disease and Cognitive Decline.” Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.	1	0	1	0	0	1	1	1	1	1	0	7 (Moderate)
Weih M et al. “Physical Activity and Alzheimer’s Disease.” GeroPsych 23.1 (2010): 17-20.	1	0	0	0	0	1	0	1	1	1	0	5 (Moderate)
Hurley BF, et al. “Strength Training as a Countermeasure to Aging Muscle and Chronic Disease.” Sports Medicine 41.4 (2011): 289-306.	1	0	0	0	0	0	0	0	N/A	0	0	1 (Low)

The ESHRE Capri Workshop Group. “Perimenopausal risk factors and future health.” Human Reproduction Update 17.5 (2011): 706 – 717.	1	0	0	0	0	0	0	0	N/A	0	0	1 (Low)
Barnes DR, et al. “The projected effect of risk factor reduction on Alzheimer’s disease prevalence.” Lancet Neurology 10 (2011): 819-828.	1	0	0	0	0	0	0	1	N/A	0	0	2 (Low)

*N/A – Not applicable because meta-analysis not conducted

¹Was an 'a priori' design provided? (1)The research question/aim and (2) inclusion criteria should be established before the conduct of the review.

²Was there duplicate study selection and data extraction? (1)There should be at least two independent data extractors and a (2) consensus procedure for disagreements should be in place.

³Was a comprehensive literature search performed? (1) At least two databases must be searched; (2) The report must include years and databases used; (3) keywords and/or MESH terms must be stated; (4) search strategy must be provided where feasible; (5) All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the field, and by reviewing the references in the studies found.

⁴Was the status of publication (i.e. grey literature) used as an inclusion criteria? (1) Authors should state they searched reports regardless of publication type; (2) Authors should state whether or not they excluded any reports (from the systematic review) based on their publication status, languages, etc.

⁵**Was a list of studies (included and excluded) provided?** A list of (1) included and (2) excluded studies should be provided.

⁶Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. Ranges of characteristics (age, sex, relevant socioeconomic data, disease status, duration , severity, or other diseases should be reported)

⁷Was the scientific quality of the included studies assessed and documented? A priori methods of assessment should be provided

⁸Was the scientific quality of the included studies used appropriately in formulating conclusions? Results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

⁹Were the methods used to combine the findings of studies appropriate? For pooled results, a test should be done to ensure studies were comparable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?)

¹⁰Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).

¹¹Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies

APPENDIX A-7: Systematic reviews included in the National Population Health Study of Neurological Conditions (n=81)

- Ahlbom A, et al. "Neurodegenerative diseases, suicide and depressive symptoms in relation to EMF." *Bioelectromagnetics Supplement* 5 (2001): S132-S143.
- Almeida OP, et al. "Smoking as a risk factor for Alzheimer's disease: contrasting evidence from a systematic review of case-control and cohort studies." *Addiction* 97.1 (2002): 15-28.
- Anstey KJ, et al. "Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies." *American Journal of Geriatric Psychiatry* 17.7 (2009): 542 – 555.
- Anstey KJ, et al. "Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies." *Obesity Reviews* 12 (2011): e426–e437.
- Anstey KJ, et al. "Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis." *American Journal of Geriatric Psychiatry* 16.5 (2008): 343 – 354.
- Anstey KJ, et al. "Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies." *American Journal of Epidemiology* 166.4 (2007): 367-78.
- Barranco Quintana JL, et al. "Alzheimer's disease and coffee: a quantitative review." *Neurological Research* 29.1 (2007): 91-5.
- Beydoun MA, et al. "Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis." *Obesity Reviews* 9 (2008): 204-218.
- Biessels GJ, et al. "Risk of dementia in diabetes mellitus: a systematic review." *Lancet Neurology* 5 (2006): 64-74.
- Breteler MMB, et al. "Medical history and the risk of Alzheimer's disease: a collaborative re-analysis of case-control studies." *International Journal of Epidemiology* 20.2 (1991).
- Cataldo JK, et al. "Cigarette smoking is a risk factor for Alzheimer's disease: an analysis controlling for tobacco industry affiliation." *Journal of Alzheimer's disease* 19 (2010): 465 - 480.
- Caamano-Isorna F, et al. "Education and dementia: a meta-analytic study." *Neuroepidemiology* 26 (2006): 226-232.
- Chang-Quan H, et al. "The association of antihypertensive medication use with risk of cognitive decline and dementia: a meta-analysis of longitudinal studies." *The International Journal of Clinical Practice* 65.12 (2011): 1295-1305.
- Crichton GE, et al. "Review of dairy consumption and cognitive performance in adults: findings and methodological issues." *Dementia & Geriatric Cognitive Disorders* 30.4 (2010): 352-61.
- Cukierman T, et al. "Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies." *Diabetologia* 48 (2005): 2460 – 2469.
- Dangour AD, et al. "B-Vitamins and fatty acids in the prevention and treatment of Alzheimer's disease and

dementia: a systematic review.” *Journal of Alzheimer’s Disease* 22 (2010): 205-224

.

Debette S, et al. “The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis.” *BMJ* 341 (2010).

de Craen AJM, et al. “Meta-Analysis of nonsteroidal antiinflammatory drug use and risk of dementia.” *American Journal of Epidemiology* 161.2 (2004): 114-120.

Di Bona D, et al. “Association between the interleukin-1 β polymorphisms and Alzheimer's disease: A systematic review and meta-analysis.” *Brain Research Reviews* 59 (2008): 155 – 163.

Di Bona D, et al. “Systematic review by meta-analyses on the possible role of TNF- α polymorphisms in association with Alzheimer’s disease.” *Brain Research Reviews* 61 (2009): 60-68.

Diniz BS, et al. “To treat or not to treat? A meta-analysis of the use of cholinesterase inhibitors in mild cognitive impairment for delaying progression to Alzheimer’s disease.” *European Archives of Psychiatry and Clinical Neuroscience* 259 (2009): 248 – 56.

Elias-Sonnenschein LS, et al. “Predictive value of APOE- ϵ 4 allele for progression from MCI to AD-type dementia: a meta-analysis.” *Journal of Neurology, Neurosurgery, & Psychiatry* 82 (2011): 1149-1156.

Elkins JS, et al. “Alzheimer disease risk and genetic variation in ACE.” *Neurology* 62 (2004): 363 – 368.

Etminan E, et al. “Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer’s disease: systematic review and meta-analysis of observational studies.” *BMJ* 327 (2003).

Fleminger S, et al. “Head injury as a risk factor for Alzheimer’s disease: the evidence 10 years on; a partial replication.” *Journal of Neurology, Neurosurgery, and Psychiatry* 74 (2003): 857-862.

Gao S et al. “The relationships between age, sex, and the incidence of dementia and Alzheimer disease.” *Archives of General Psychiatry* 55 (1998): 809-15.

Garcia AM, et al. “Occupational exposure to extremely low frequency electric and magnetic fields and Alzheimer disease: a meta-analysis.” *International Journal of Epidemiology* 37 (2008): 329-340.

Gorospe EC, et al. “The risk of dementia with increased body mass index.” *Age and Ageing* 36 (2007): 23-9.

Graves AB, et al. "Alcohol and tobacco consumption as risk factors for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group." *International Journal of Epidemiology* 20 Suppl 2.(1991): S48-57.

Graves AB, et al. “Occupational exposures to solvents and lead as risk factors for Alzheimer’s disease: a collaborative re-analysis of case-control studies.” *International Journal of Epidemiology* 20.2 (1991).

Guerchet M, et al. “Ankle-brachial index as a marker of cognitive impairment and dementia in general population. A systematic review.” *Atherosclerosis* 216 (2011): 251-257.

Hamer M and Chida Y. "Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence." *Psychological Medicine* 39.1 (2009): 3-11.

Han XM, et al. “Interleukin-6 -174G/C polymorphism and the risk of Alzheimer’s disease in Caucasians: A

meta-analysis.” *Neuroscience Letters* 504 (2011): 4-8.

Hao Z, et al. “Association between metabolic syndrome and cognitive decline: a systematic review of prospective population-based studies.” *Acta Neuropsychiatrica* 23 (2011): 69–74.

Hao P, et al. “Meta-analysis of aldehyde dehydrogenase 2 gene polymorphism and Alzheimer’s disease in East Asians.” *Canadian Journal of Neurological Sciences* 38 (2011): 500 – 506.

Ho RC, et al. “Is high homocysteine level a risk factor for cognitive decline in elderly? A systematic review, meta-analysis, and meta-regression.” *American Journal of Geriatric Psychiatry* 19.7 (2011): 607-17.

Hua Y, et al. “Association Between the MTHFR Gene and Alzheimer’s Disease: A Meta-Analysis.” *International Journal of Neuroscience* 121 (2011): 462-471.

Issa AM, et al. “The efficacy of omega-3 fatty acids on cognitive function in aging and dementia: a systematic review.” *Dementia & Geriatric Cognitive Disorders* 21.2 (2006): 88-96.

Kloppenborg RP, et al. “Diabetes and other vascular risk factors for dementia: Which factor matters most? A systematic review.” *European Journal of Pharmacology* 585 (2008): 97-108.

Kuo HK, et al. “Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: systematic review and meta-analysis.” *Lancet Neurology* 4 (2005): 371-380.

LeBlanc ES, et al. “Hormone replacement therapy and cognition.” *Journal of the American Medical Association* 285.11 (2001): 1489 – 1499.

Lee Y, et al. “Systematic review of health behaviour risks and cognitive health in older adults.” *International Psychogeriatrics* 22.2 (2010): 174-187.

Lim WS, et al. “Omega 3 fatty acid for the prevention of dementia.” *Cochrane Database of Systematic Reviews* 1 (2006): CD005379.

Llorca J, et al. “Meta-analysis of genetic variability in the beta-amyloid production, aggregation and degradation metabolic pathways and the risk of Alzheimer’s disease.” *Acta Neurologica Scandinavica* 117 (2008): 1-14.

Lu FP, et al. “Diabetes and the risk of multi-system aging phenotypes: a systematic review and meta-analysis.” *PLoS One* 4.1 (2009).

Mitchell AJ, et al. “Rate of progression of mild cognitive impairment to dementia – meta-analysis of 41 robust inception cohort studies.” *Acta Psychiatrica Scandinavica* 119 (2009): 252-65.

Mortimer JA, et al. “Head trauma as a risk factor for alzheimer’s disease: a collaborative re-analysis of case-control studies.” *International Journal of Epidemiology* 20.2 (1991): S28-S35.

Ning M, et al. “Amyloid- β -related genes SORL1 and ACE are genetically associated with risk for late-onset Alzheimer disease in the Chinese population.” *Alzheimer Disease and Related Disorders* 24.4 (2010): 390-396.

Ntais C, et al. “Meta-analysis of the association of the cathepsin D Ala224Val gene polymorphism with the risk of Alzheimer’s disease: A HuGE gene-disease association review.” *American Journal of Epidemiology*

159.6(2004): 527-536.

Ownby R, et al. "Depression and risk for Alzheimer disease." *Arch Gen Psychiatry* 63 (2006): 530-538.

Patterson C, et al. "General risk factors for dementia: A systematic evidence review." *Alzheimer's and Dementia* 3 (2007): 341-7.

Peters R, et al. "Alcohol, dementia and cognitive decline in the elderly: a systematic review." *Age & Ageing* 37.5 (2008): 505-12.

Peters R, et al. "Haemoglobin, anaemia, dementia and cognitive decline in the elderly, a systematic review." *BMI Geriatrics* 8:18 (2008).

Peters R, et al. "Smoking, dementia and cognitive decline in the elderly, a systematic review." *BMC Geriatrics* 8:36 (2008).

Power MC, et al. "The association between blood pressure and incident Alzheimer disease: a systematic review and meta-analysis." *Epidemiology* 22.5 (2011): 646-659.

Podewils LJ. Physical activity and dementia risk: A prospective study. Dissertation, Johns Hopkins University, 2003. Web.

Profenno LA, et al. "Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders." *Biological Psychiatry* 67 (2010) 505-512.

Rainero I, et al. "Association between the interleukin-1 α gene and Alzheimer's disease: a meta-analysis." *Neurobiology of Aging* 25 (2004): 1293-8.

Raman G, et al. "Heterogeneity and lack of good quality studies limit association between folate, vitamins B-6 and B-12, and cognitive function." *Journal of Nutrition* 137 (2007): 1789-94.

Raschetti R, et al. "Cholinesterase inhibitors in Mild Cognitive Impairment: a systematic review of randomised trials." *PLoS Medicine* 4.11 (2007).

Rocca WA, et al. "Maternal age and Alzheimer's disease: a collaborative re-analysis of case-control studies." *International Journal of Epidemiology* 20.2 (1991): S21-S27.

Rodriguez-Manotas R, et al. "Association study and meta-analysis of Alzheimer's disease risk and presenilin-1 intronic polymorphism." *Brain Research* 1170 (2007): 119 – 128.

Rolland Y., Abellan van Kan G. and Vellas B. "Physical activity and Alzheimer's disease: from prevention to therapeutic perspectives". *Journal of the American Medical Directors Association* 9.6 (2008): 390-405.

Reitz C, "Meta-analysis of the association between variants in SORL1 and Alzheimer disease." *Archives of Neurology* 68.1 (2011): 99-106.

Santibanez M, et al. "Occupational risk factors in Alzheimer's disease: a review assessing the quality of published epidemiological studies." *Occupational and Environmental Medicine* 64 (2007): 723-732.

Santos C, et al. "Caffeine intake and dementia: systematic review and meta-analysis." *Journal of Alzheimer's Disease* 20 Suppl 1.(2010): S187-204.

- Shah K, et al. "Does use of antihypertensive drugs affect the incidence or progression of dementia? A systematic review." *The American Journal of Geriatric Pharmacotherapy* 7 (2009): 250-261.
- Sofi F, et al. "Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis." *American Journal of Clinical Nutrition* 92.5 (2010): 1189-96.
- Sofi F, et al. "Adherence to Mediterranean diet and health status: meta-analysis." *BMJ* 337.(2008): a1344.
- Stern C, et al. "Cognitive leisure activities and their role in preventing dementia: a systematic review." *International Journal of Evidence Based Healthcare* 8 (2010): 2-17."
- Stern C and Konno R. "Physical leisure activities and their role in preventing dementia: a systematic review." *International Journal of Evidence-Based Healthcare* 7.4 (2009): 270-82.
- Szekely C, et al. "Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: a systematic review." *Neuroepidemiology* 23 (2004): 159 – 169.
- van Duijn CM, et al. "Familial aggregation of Alzheimer's disease and related disorders: a collaborative re-analysis of case-control studies." *International Journal of Epidemiology* 20.2 (1991).
- Williams JW, et al. "Preventing Alzheimer's Disease and Cognitive Decline." Evidence Report/Technology Assessment N0. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.
- Weih M, et al. "Non-pharmacologic prevention of Alzheimer's disease: nutritional and life-style risk factors." *Journal of Neural Transmission* 114 (2007): 1187-1197.
- Weih M., et al. "Physical activity and alzheimer's disease: A meta-analysis of cohort studies". *GeroPsych: The Journal of Gerontopsychology and Geriatric Psychiatry* 23.1 (2010): 17-20.
- Xin X, et al. "Apolipoprotein E promoter polymorphisms and risk of Alzheimer's disease: evidence from meta-analysis." *Journal of Alzheimer's Disease* 19 (2010): 1283 – 1294.
- Yaffe K, et al. "Estrogen therapy in postmenopausal women." *Journal of the American Medical Association* 279.9 (1998): 688 – 695.
- Zhang M, et al. "Meta-analysis of the methylenetetrahydrofolate reductase C677T polymorphism and susceptibility to Alzheimer's disease." *Neuroscience Research* 68 (2010): 142-150.
- Zhang Y, "The -1082G/A polymorphism in IL-10 gene is associated with risk of Alzheimer's disease: A meta-analysis." *Journal of the Neurological Sciences* 303 (2011): 133-8.
- Zhou B, et al. "Prevention and treatment of dementia or Alzheimer's disease by statins: a meta-analysis." *Dementia and Geriatric Cognitive Disorders* 23 (2007): 194-201.

APPENDIX B-1: Literature Search Strategy

Database: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process	
Date of Search:	15 Sept. 2013
Years Searched:	2009 – Sept 2013
Alerts:	None
Limits:	Year limit (2009 – Sept. 2013)
Filters:	None
Search Strategy:	
Line #	Strategy
1	Mediterranean diet.mp. or Diet, Mediterranean/
2	Diet/ or diet.mp.
3	Food Habits/ or dietary pattern.mp.
4	Mediterranean.mp.
5	adherence.mp.
6	score.mp.
7	1 or 2 or 3 or 4 or 5 or 6
8	alzheimer disease/ or dementia/
9	(Alzheimer* or presenile dementia* or acute confusional senile dementia or Senile dementia* or primary senile degenerative dementia or primary degenerative senile).mp.
10	8 or 9
11	prospective.mp. or Prospective Studies/
12	Follow-Up Studies/ or follow-up.mp.
13	Cohort Studies/ or cohort.mp.
14	11 or 12 or 13
15	7 and 10
16	14 and 15
17	limit 16 to yr="2009 -Current"

Database: Ovid EMBASE Classic + EMBASE	
Date of Search:	15 Sept. 2013
Years Searched:	2009 – Sept. 2013
Alerts:	None
Limits:	Year Limit (2009 – Sept. 2013)
Filters:	None
Search Strategy:	
Line #	Strategy
1	Mediterranean diet.mp. or Mediterranean diet/
2	diet/ or diet.mp.
3	dietary intake/ or food intake/ or dietary pattern.mp.
4	Mediterranean.mp.
5	adherence.mp.
6	score.mp.
7	1 or 2 or 3 or 4 or 5 or 6

8	alzheimer disease/ or dementia/
9	alzheimer*.mp.
10	8 or 9
11	prospective study/ or prospective.mp.
12	follow-up.mp. or follow up/
13	cohort analysis/ or cohort.mp.
14	11 or 12 or 13
15	7 and 10
16	14 and 15
17	limit 16 to yr="2009 -Current"

Database: Ovid PsycINFO	
Date of Search:	15 Sept. 2013
Years Searched:	2009 – Sept. 2013
Alerts:	None
Limits:	Year Limit (2009 – Sept. 2013)
Filters:	None
Search Strategy:	
Line #	Strategy
1	Mediterranean diet.mp.
2	Diet.mp. or Diets/
3	Eating Behavior/ or Food Intake/ or Dietary pattern.mp.
4	Mediterranean.mp.
5	adherence.mp.
6	score.mp.
7	1 or 2 or 3 or 4 or 5 or 6
8	Dementia/ or Alzheimer's Disease/
9	(Alzheimer* or presenile dementia* or acute confusional senile dementia or Senile dementia* or primary senile degenerative dementia or primary degenerative senile).mp.
10	8 or 9
11	Prospective Studies/ or prospective.mp.
12	Followup Studies/ or follow-up.mp.
13	Cohort Analysis/ or cohort.mp.
14	11 or 12 or 13
15	7 and 10
16	14 and 15
17	limit 16 to yr="2009 -Current"

Database: EBSCO CINAHL	
Date of Search:	15 Sept. 2013
Years Searched:	2009 – Sept. 2013
Alerts:	None
Limits:	Year Limit (2009 – Sept. 2013)
Filters:	None
Search Strategy:	

Line #	Strategy
1	(MH "Mediterranean Diet") OR "Mediterranean diet"
2	(MH "Diet") OR "diet"
3	"dietary pattern"
4	"Mediterranean"
5	"adherence"
6	"score"
7	S1 OR S2 OR S3 OR S4 or S5 OR S6
8	(MH "Alzheimer's Disease")
9	"Alzheimer*"
10	S8 OR S9
11	(MH "Prospective Studies") OR "prospective"
12	"follow-up"
13	"cohort analysis"
14	"cohort stud*"
15	S11 OR S12 OR S13 OR S14
16	S7 AND S10
17	S15 AND S16 [Limiters – Published Date: 20090101 – 20130931]

Database:	EBSCO AARP Ageline
Date of Search:	15 Sept. 2013
Years Searched:	2009 – Sept. 2013
Alerts:	None
Limits:	Year Limits (2009 – Sept. 2013)
Filters:	None
Search Strategy:	
Line #	Strategy
1	Mediterranean diet
2	diet
3	Dietary pattern
4	Mediterranean
5	Adherence
6	Score
7	S1 OR S2 OR S3 OR S4 OR S5 OR S6
8	Alzheimer's Disease OR presenile dementia* OR acute confusional senile dementia OR Senile dementia* OR primary senile degenerative dementia OR primary degenerative senile
9	Prospective stud*
10	Prospective
11	Follow-up
12	Cohort stud*
13	S9 OR S10 OR S11 OR S12
14	S7 AND S8
15	S13 AND S14 [Limiters – Publication Year: 2009 -]

Database:	Web of Science
Date of Search:	15 Sept. 2013
Years Searched:	2009 – Sept 2013

Alerts:	None
Limits:	Year limit (2009 – 2013)
Filters:	None
Search Strategy:	
Line #	Strategy
1	Topic=Mediterranean diet) OR Topic=(diet) OR Topic=(dietary pattern) OR Topic=(adherence) OR Topic=(score)
2	Topic=(Alzheimer's disease) OR Topic=(Alzheimer*) OR Topic=(presenile dementia*) OR Topic=(acute confusional senile dementia) OR Topic=(senile dementia*) OR Topic=(primary senile degenerative dementia) OR Topic=(primary degenerative senile)
3	Topic=(prospective) OR Topic=(prospective stud*) OR Topic=(follow-up stud*) OR Topic=(cohort stud*)
4	#2 AND #1
5	#4 AND #3 [Timespan = 2009-2013]

Database:	The Cochrane Library (The Cochrane Central Register of Controlled Trials)
Date of Search:	15 Sept. 2013
Years Searched:	2009 – Sept 2013
Alerts:	None
Limits:	Year limit (2009 – 2013)
Filters:	None
Search Strategy:	
Line #	Strategy
1	Mediterranean diet
2	MeSH descriptor: [Diet, Mediterranean] explode all trees.
3	Diet
4	MeSH descriptor: [Diet] explode all trees
5	Dietary pattern
6	MeSH descriptor: [Food Habits] explode all trees
7	Mediterranean
8	Adherence
9	Score
10	#1 OR #2 or #3 OR #4 OR #5 OR # 6 OR #7 OR #8 OR #9
11	Alzheimer*
12	MeSH descriptor: [Alzheimer Disease] explode all trees
13	(presenile dementia*) or (acute confusional senile dementia) or (Senile dementia*) or (primary senile degenerative dementia) or (primary degenerative senile)
14	#11 OR # 12 OR #13
15	#10 AND #14 (from 2009 to 2013, in Trials) - Cochrane Central Register of Controlled Trials : Issue 8 of 12, August 2013

Database:	Clinicaltrials.gov
Date of Search:	15 Sept. 2013
Years Searched:	2009 – Sept 2013
Alerts:	None

Limits:	Year limit (2009 – 2013)
Filters:	None
Search Strategy:	
Line #	Strategy
1	Condition: Alzheimer*
2	Intervention: Mediterranean* OR diet
3	First received: 01/01/2009 to 09/15/2013

Database:	International Journal of Alzheimer's Disease
Date of Search:	10 Oct. 2013
Years Searched:	2009 – 10 Oct. 2013
Alerts:	None
Limits:	None
Filters:	Observational study filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	No search engine available, therefore, all five volumes of the journal (2009, 2010, 2011, 2012, 2013) were scanned. Articles deemed potentially relevant were selected.

Database:	American Journal of Alzheimer's Disease and Other Dementias (SAGE Journals Online)
Date of Search:	10 Oct. 2013
Years Searched:	1986 – 10 Oct. 2013
Alerts:	None
Limits:	None
Filters:	Observational study filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	Mediterranean diet

Database:	Google
Date of Search:	10 Oct. 2013
Years Searched:	N/A
Alerts:	None
Limits:	None
Filters:	Observational study filter: None Etiology/Risk filter: None

Search Strategy:	
Line #	Strategy
1	"Alzheimer's Disease" OR "presenile dementia" OR "acute confusional senile dementia" OR "Senile dementia" OR "primary senile degenerative dementia" OR "primary degenerative senile" AND "risk" OR "risk factor" OR "etiology" AND "Mediterranean diet" <i>First 10 pages scanned for relevant articles.</i>

Database:	GoogleScholar
Date of Search:	10 Oct. 2013
Years Searched:	N/A
Alerts:	None
Limits:	None
Filters:	Observational study filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	"Alzheimer's Disease" OR "presenile dementia" OR "acute confusional senile dementia" OR "Senile dementia" OR "primary senile degenerative dementia" OR "primary degenerative senile" AND "risk" OR "risk factor" OR "etiology" AND "Mediterranean diet" <i>First 10 pages scanned for relevant articles.</i>

Database:	ProQuest Dissertation and Theses
Date of Search:	10 Oct. 2013
Years Searched:	1861 – 10 Oct. 2013
Alerts:	None
Limits:	None
Filters:	Systematic review filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	ab(alzheimer's disease OR presenile dementia OR acute confusional senile dementia OR senile dementia* or primary degenerative dementia OR primary degenerative senile) AND ab(Mediterranean diet) AND ab(cohort OR prospective)

APPENDIX B-2: Excluded studies (n=68) following full-article screening

Study	Reason for exclusion
Akbaraly TN, et al. "Education attenuates the association between dietary patterns and cognition." <i>Dementia & Geriatric Cognitive Disorders</i> 27.2 (2009): 147-54.	Does not examine Mediterranean diet
Arab L and Sabbagh MN. "Are certain lifestyle habits associated with lower Alzheimer's disease risk?." <i>Journal of Alzheimer's Disease</i> 20.3 (2010): 785-94.	Review
Barberger-Gateau P, et al. "Dietary patterns and risk of dementia: the Three-City cohort study." <i>Neurology</i> 69.20 (2007): 1921-30.	Does not examine Mediterranean diet
Blumenthal JA, Babyak MA and Sherwood A. "Diet, exercise habits, and risk of Alzheimer disease." <i>JAMA</i> 302.22 (2009): 2431.	Commentary/editorial with no primary data
Chen X, Huang Y and Cheng HG. "Lower intake of vegetables and legumes associated with cognitive decline among illiterate elderly Chinese: a 3-year cohort study." <i>Journal of Nutrition, Health & Aging</i> 16.6 (2012): 549-52.	Does not examine Mediterranean diet
Cherbuin N., Kumar R. and Anstey K.. "Caloric intake, but not the mediterranean diet, is associated with cognition and mild cognitive impairment". Conference: Alzheimer's Association International Conference, AAIC 11 Paris France. Conference Start: 20110716 Conference End: 20110721 Conference Publication: (var.pagings) <i>Alzheimer's and Dementia</i> 7.4 SUPPL. 1 (2011): S691.	Does not report on risk of developing AD
Corley J, et al. "Do dietary patterns influence cognitive function in old age?." <i>International Psychogeriatrics</i> 25.9 (2013): 1393-407.	Does not examine Mediterranean diet
Daviglus ML, et al. "Risk factors and preventive interventions for Alzheimer disease: state of the science." <i>Archives of Neurology</i> 68.9 (2011): 1185-90.	Review
Devore EE, et al. "Total antioxidant capacity of the diet and major neurologic outcomes in older adults." <i>Neurology</i> 80.10 (2013): 904-10.	Does not examine Mediterranean diet
Devore EE, et al. "Total antioxidant capacity of diet in relation to cognitive function and decline." <i>American Journal of Clinical Nutrition</i> 92.5 (2010): 1157-64.	Does not examine Mediterranean diet
Dosunmu R, et al. "Environmental and dietary risk factors in Alzheimer's disease." <i>Expert Review of Neurotherapeutics</i> 7.7 (2007): 887-900.	Review
Eskelinen M.H., et al. "Healthy diet at midlife and the risk of late-life dementia and Alzheimer's disease: A population-based CAIDE	Does not examine Mediterranean diet

study". Conference: Alzheimer's Association International Conference on Alzheimer's Disease Vienna Austria. Conference Start: 20090711 Conference End: 20090716 Conference Publication: (var.pagings) Alzheimer's and Dementia 5.4 SUPPL. 1 (2009): 284.	
Feart C., Samieri C. and Barberger-Gateau P.. "Mediterranean diet and cognitive decline - Reply". JAMA - Journal of the American Medical Association 302.22 (2009): 2432.	Commentary/editorial with no primary data
Feart C, et al. "Adherence to a Mediterranean diet and onset of disability in older persons." European Journal of Epidemiology 26.9 (2011): 747-56.	Does not report on risk of developing AD
Feart C, et al. "Mediterranean diet and cognitive function in older adults." Current Opinion in Clinical Nutrition & Metabolic Care 13.1 (2010): 14-8.	Review
Feart C, et al. "Adherence to a Mediterranean diet, cognitive decline, and risk of dementia." JAMA 302.6 (2009): 638-48.	Included in review reported by Sofi et al.
Feart C, et al. "Adherence to a Mediterranean diet and plasma fatty acids: data from the Bordeaux sample of the Three-City study." British Journal of Nutrition 106.1 (2011): 149-58.	Does not report on risk of developing AD
Flicker L. "Modifiable lifestyle risk factors for Alzheimer's disease." Journal of Alzheimer's Disease 20.3 (2010): 803-11.	Review
Frisardi V, et al. "Nutraceutical properties of Mediterranean diet and cognitive decline: possible underlying mechanisms." Journal of Alzheimer's Disease 22.3 (2010): 715-40.	Review
Gallucci M, et al. "Body mass index, lifestyles, physical performance and cognitive decline: the "Treviso Longeva (TRELONG)" study." Journal of Nutrition, Health & Aging 17.4 (2013): 378-84.	Does not report on risk of developing AD
Gardener S, et al. "Adherence to a Mediterranean diet and Alzheimer's disease risk in an Australian population." Transl Psychiatry Psychiatry 2.(2012): e164.	Cross-sectional study
Gu Y., et al. "A dietary pattern associated with reduced risk of Alzheimer's disease". Conference: Alzheimer's Association International Conference on Alzheimer's Disease Vienna Austria. Conference Start: 20090711 Conference End: 20090716 Conference Publication: (var.pagings) Alzheimer's and Dementia 5.4 SUPPL. 1 (2009): 282.	Does not examine Mediterranean diet
Gu Y, et al. "Food combination and Alzheimer disease risk: a protective diet." Archives of Neurology 67.6 (2010): 699-706.	Does not examine Mediterranean diet
Gu Y and Scarmeas N. "Dietary patterns in Alzheimer's disease and cognitive aging." Current Alzheimer Research 8.5 (2011): 510-9.	Review
Hu N, et al. "Nutrition and the risk of Alzheimer's disease." BioMed Research International 2013.(2013): 524820.	Review

Kamphuis PJ and Scheltens P. "Can nutrients prevent or delay onset of Alzheimer's disease?." <i>Journal of Alzheimer's Disease</i> 20.3 (2010): 765-75.	Review
Katsiardanis K, et al. "Cognitive impairment and dietary habits among elders: the Velestino Study." <i>Journal of Medicinal Food</i> 16.4 (2013): 343-50.	Does not report on risk of developing AD
Kawas CH. "Diet and the risk for Alzheimer's disease." <i>Annals of Neurology</i> 59.6 (2006): 877-9.	Review
Kayyali A, et al. "Diet and exercise reduce Alzheimer's risk." <i>American Journal of Nursing</i> 110.2 (2010): 65.	Review
Kesse-Guyot E, et al. "A healthy dietary pattern at midlife is associated with subsequent cognitive performance." <i>Journal of Nutrition</i> 142.5 (2012): 909-15.	Does not examine Mediterranean diet
Kesse-Guyot E, et al. "Mediterranean diet and cognitive function: a French study." <i>American Journal of Clinical Nutrition</i> 97.2 (2013): 369-76.	Does not report on risk of developing AD
KnopmanD.S.. "Association between Mediterranean diet and late-life cognition - Reply". <i>JAMA - Journal of the American Medical Association</i> 302.22 (2009): 2433.	Does not report on risk of developing AD
Lee Y, Kim J and Back JH. "The influence of multiple lifestyle behaviors on cognitive function in older persons living in the community." <i>Preventive Medicine</i> 48.1 (2009): 86-90. Ovid MEDLINE(R).	Does not examine Mediterranean diet
Liebson PR. "Diet, lifestyle, and hypertension and mediterranean diet and risk of dementia." <i>Preventive Cardiology</i> 13.2 (2010): 94-6.	Review
Lourida I, et al. "Mediterranean diet, cognitive function, and dementia: a systematic review." <i>Epidemiology</i> 24.4 (2013): 479-89.	Review
Morris MC and Tangney CC. "Diet and prevention of Alzheimer disease." <i>JAMA</i> 303.24 (2010): 2519-20.	Commentary/editorial with no primary data
Norton MC, et al. "Lifestyle behavior pattern is associated with different levels of risk for incident dementia and Alzheimer's disease: the Cache County study." <i>Journal of the American Geriatrics Society</i> 60.3 (2012): 405-12.	Does not examine Mediterranean diet
Ochner C.N., et al. "Evidence on diet modification for Alzheimer's disease and mild cognitive impairment". Conference: 5th Conference Clinical Trials on Alzheimer's Disease Monte Carlo Monaco. Conference Start: 20121029 Conference End: 20121031 Conference Publication: (var.pagings) <i>Journal of Nutrition, Health and Aging</i> 16.9 (2012): 860-861.	Review

Olsson E, et al. "Dietary pattern and cognitive disorders in a 12-year follow-up study of 70 year old men." <i>Clinical Nutrition Supplements</i> 6.1 (2011): 209-10.	Full-text could not be obtained (not yet published)
Panza F, et al. "Mediterranean diet, mild cognitive impairment, and Alzheimer's disease." <i>Experimental Gerontology</i> 42.1-2 (2007): 6-7.	Commentary/editorial with no primary data
Panza F, et al. "Mediterranean diet and cognitive decline." <i>Public Health Nutrition</i> 7.7 (2004): 959-63.	Review
Peneau S, et al. "Fruit and vegetable intake and cognitive function in the SU.VI.MAX 2 prospective study." <i>American Journal of Clinical Nutrition</i> 94.5 (2011): 1295-303.	Does not examine Mediterranean diet
Perez-Lopez FR, et al. "Effects of the Mediterranean diet on longevity and age-related morbid conditions." <i>Maturitas</i> 64.2 (2009): 67-79.	Review
Peters R. "The prevention of dementia." <i>International Journal of Geriatric Psychiatry</i> 24.5 (2009): 452-8.	Review
Peters R, et al. "Sociodemographic and lifestyle risk factors for incident dementia and cognitive decline in the HYVET." <i>Age & Ageing</i> 38.5 (2009): 521-7.	Does not examine Mediterranean diet
Reynish W, et al. "Nutritional factors and Alzheimer's disease." <i>Journals of Gerontology Series A-Biological Sciences & Medical Sciences</i> 56.11 (2001): M675-80.	Review
Roberts RO, et al. "Relative intake of macronutrients impacts risk of mild cognitive impairment or dementia." <i>Journal of Alzheimer's Disease</i> 32.2 (2012): 329-39.	Does not examine Mediterranean diet
Roman B, et al. "Effectiveness of the Mediterranean diet in the elderly." <i>Clinical Interventions In Aging</i> 3.1 (2008): 97-109.	Review
Samieri C, et al. "Long-term adherence to the Mediterranean diet is associated with overall cognitive status, but not cognitive decline, in women." <i>Journal of Nutrition</i> 143.4 (2013): 493-9.	Does not report on risk of developing AD
Scarmeas N., et al. "Food combination and Alzheimer's Disease (AD) risk: A Dietary Pattern (DP) approach". Conference: 134th American Neurological Association, ANA Meeting Baltimore, MD United States. Conference Start: 20091011 Conference End: 20091014 Conference Publication: (var.pagings) <i>Annals of Neurology</i> 66.(2009): S43-S44.	Does not examine Mediterranean diet
Scarmeas N, et al. "Mediterranean diet and mild cognitive impairment." <i>Archives of Neurology</i> 66.2 (2009): 216-25.	Included in review reported by Sofi et al. (also reports on conversion from MCI to AD)
Scarmeas N, et al. "Mediterranean diet and risk for Alzheimer's disease." <i>Annals of Neurology</i> 59.6 (2006): 912-21.	Included in review reported by Sofi et

	al.
Shatenstein B, et al. "Diet quality and cognition among older adults from the NuAge study." <i>Experimental Gerontology</i> 47.5 (2012): 353-60.	Does not examine Mediterranean diet
Sofi F, et al. "Effectiveness of the Mediterranean diet: can it help delay or prevent Alzheimer's disease?." <i>Journal of Alzheimer's Disease</i> 20.3 (2010): 795-801.	Review
Solfrizzi V, et al. "Mediterranean diet in predementia and dementia syndromes." <i>Current Alzheimer Research</i> 8.5 (2011): 520-42.	Review
Solfrizzi V, Panza F and Capurso A. "The role of diet in cognitive decline." <i>Journal of Neural Transmission</i> 110.1 (2003): 95-110.	Review
Takechi R, et al. "Dietary fats, cerebrovasculature integrity and Alzheimer's disease risk." <i>Progress in Lipid Research</i> 49.2 (2010): 159-70.	Review
Tangney CC, et al. "Adherence to a Mediterranean-type dietary pattern and cognitive decline in a community population." <i>American Journal of Clinical Nutrition</i> 93.3 (2011): 601-7.	Does not report on risk of developing AD
Tripathi M, et al. "Risk factors of dementia in North India: a case-control study." <i>Aging & Mental Health</i> 16.2 (2012): 228-35.	Does not examine Mediterranean diet
Tsivgoulis G, et al. "Adherence to a Mediterranean diet and risk of incident cognitive impairment." <i>Neurology</i> 80.18 (2013): 1684-92.	Does not report on risk of developing AD
Valenzuela M, et al. "Cognitive lifestyle and long-term risk of dementia and survival after diagnosis in a multicenter population-based cohort." <i>American Journal of Epidemiology</i> 173.9 (2011): 1004-12.	Does not examine Mediterranean diet
Valls-Pedret C, et al. "Polyphenol-rich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk." <i>Journal of Alzheimer's Disease</i> 29.4 (2012): 773-82.	Does not report on risk of developing AD
Vercambre MN, et al. "Long-term association of food and nutrient intakes with cognitive and functional decline: a 13-year follow-up study of elderly French women." <i>British Journal of Nutrition</i> 102.3 (2009): 419-27.	Does not examine Mediterranean diet
Vercambre MN, et al. "Mediterranean diet and cognitive decline in women with cardiovascular disease or risk factors." <i>Journal of the Academy of Nutrition & Dietetics</i> 112.6 (2012): 816-23.	Does not report on risk of developing AD
Walach H. and Loef M.. "The effects of a healthy lifestyle on Alzheimer's disease". Conference: Alzheimer's Association International Conference 2012 Vancouver, BC Canada. Conference Start: 20120714 Conference End: 20120719 Conference Publication: (var.pagings) <i>Alzheimer's and Dementia</i> 8.4 SUPPL. 1 (2012): P147.	Review

Wallin K, et al. "Risk factors for incident dementia in the very old." <i>International Psychogeriatrics</i> 25.7 (2013): 1135-43.	Does not examine Mediterranean diet
Wengreen HJ, et al. "Diet quality is associated with better cognitive test performance among aging men and women." <i>Journal of Nutrition</i> 139.10 (2009): 1944-9.	Does not examine Mediterranean diet
Ye X, et al. "Variety in fruit and vegetable intake and cognitive function in middle-aged and older Puerto Rican adults." <i>British Journal of Nutrition</i> 109 (2013): 503-10.	Does not examine Mediterranean diet

APPENDIX C-1: Literature Search Strategy

OVERVIEW	
Databases:	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations Ovid MEDLINE(R) Ovid EMBASE Classic + EMBASE EBSCO CINAHL, EBSCO AARP Ageline
Date of Search:	15 July 2012
Alerts:	None
Study Types:	Case-control, Cohort
Limits:	Language limits: English or French Human population

SYNTAX GUIDE		
OVID		
AND	AND operator	Includes both terms
OR	OR operator	Includes either both, the one or the other term
/	Subject Heading	
.ab.	Abstract word	
.tw.	Text Word	Word in title or abstract field
.fs.	Floating subheading	Subheading of any Subject Heading
.pt.	Publication type	
.sh.	Subject Heading	
.mp.		Will search in title, abstract and in Subject Heading field
exp	Explode	Will include narrower terms to the Subject Heading being exploded
\$	Truncation/wild card	Adds non or more characters
\$n	Truncation/wild card	Adds non to <i>n</i> characters
?	Truncation/wild card	Adds non or one character
adj	Adjacency	Requires words are adjacent to each other in the order typed in
adjn	Adjacency	Requires words are adjacent with <i>n</i> words in between - regardless of word order
” – ”	Double quotation mark	Exact phrase searching
EBSCO		
MH	CINAHL Heading	
?	Wildcard	Replaces a single character
*	Truncation	Adds none or more characters
Nn	Near operator	N5 finds the words if they are within five

		words of one another regardless of word order
Wn	Within operator	W5 finds the words if they are within five words of one another and in the order typed in
“ - “	Double quotation mark	Exact phrase searching
Cochrane Library		
AND	AND operator	Includes both terms
OR	OR operator	Includes either both, the one or the other term
MeSH descriptor	Subject Heading	
:ti	Title word	
:ab	Abstract word	
*	Truncation	Adds non or more characters
NEAR/n	NEAR operator	Requires words are adjacent with <i>n</i> words in between - regardless of word order
NEXT	NEXT operator	Requires words are adjacent to each other in the order typed in

Syntax Guide source: *The Cochrane Effective Practice and Organisation of Care (EPOC) Group, EPOC format for reporting the search process: Database Syntax Guide, The Cochrane Effective Practice and Organisation of Care (EPOC) Group, Web, 27 Sept. 2011, table.*

Template source: Kaunelis, D. and Farrah, K. “Lecture: Introduction to Literature Searching.” Canadian Agency for Drugs and Technologies in Health (CADTH). University of Ottawa. 12 May 2011.

Database: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process	
Date of Search:	20 July 2012
Years Searched:	1948 – 20 July 2012
Alerts:	None
Limits:	Language (English, French) Human subjects
Filters:	Observational study search filter: <i>Scottish Intercollegiate Guidelines Network (SIGN)</i> . “Search Filters.” <i>Search Filters</i> . Health Improvement Scotland. 27 Feb. 2012. Web. 7 June 2012. Etiology/risk filter: Sikora, Lindsey. “Neurology Project – Alzheimer’s Disease.” Message to Mona Hersi. 16 May 2011. Email.
Search Strategy:	
Line #	Strategy
1	alzheimer disease/ or dementia/
2	(Alzheimer* or presenile dementia* or acute confusional senile dementia or Senile dementia* or primary senile degenerative dementia or primary degenerative senile).mp.
3	1 or 2

4	exp Risk/
5	etiology.fs.
6	genetic.fs.
7	prevention& control.fs.
8	4 or 5 or 6 or 7
9	Epidemiologic studies/
10	exp case control studies/
11	exp cohort studies/
12	Case control.tw.
13	(cohort adj (study or studies)).tw.
14	Cohort analy\$.tw.
15	(Follow up adj (study or studies)).tw.
16	(observational adj (study or studies)).tw.
17	Longitudinal.tw.
18	Retrospective.tw.
19	Cross-sectional studies/
20	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	Stress Disorders, Traumatic/ or Stress Disorders, Post-Traumatic/ or Stress Disorders, Traumatic, Acute/ or Stress, Psychological/ or stress.mp.
22	distress.mp.
23	Anxiety/ or Anxiety Disorders/ or anxiety.mp.
24	21 or 22 or 23
25	8 and 24
26	3 and 25
27	limit 26 to humans
28	20 and 27
29	limit 28 to (english or french)

Database: Ovid EMBASE Classic + EMBASE	
Date of Search:	20 July 2012
Years Searched:	1947 – 20 July 2012
Alerts:	None
Limits:	Language (English, French) Human subjects
Filters:	Observational study search filter: <i>Scottish Intercollegiate Guidelines Network (SIGN)</i> . “Search Filters.” <i>Search Filters</i> . Health Improvement Scotland. 27 Feb. 2012. Web. 7 June 2012.
Search Strategy:	
Line #	Strategy
1	clinical study/
2	case control study/
3	family study/
4	longitudinal study/
5	retrospective study/
6	prospective study/
7	randomized controlled trials/
8	6 not 7
9	cohort analysis/

10	(cohort adj (study or studies)).mp.
11	(case control adj (study or studies)).tw.
12	(follow up adj (study or studies)).tw.
13	(observational adj (study or studies)).tw.
14	(epidemiologic\$ adj (study or studies)).tw.
15	1 or 2 or 3 or 4 or 5 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	exp risk/
17	exp risk factor/
18	etiology/ or "general aspects of disease"/
19	"prevention and control"/
20	16 or 17 or 18 or 19
21	alzheimer disease/ or dementia/
22	alzheimer*.mp.
23	21 or 22
24	chronic stress/ or mental stress/ or stress/ or emotional stress/ or family stress/ or job stress/ or early life stress/ or acute stress disorder/ or life stress/ or acute stress/ or stress.mp. or posttraumatic stress disorder/
25	psychological stress.mp.
26	anxiety/ or anxiety.mp. or anxiety disorder/
27	24 or 25 or 26
28	20 and 27
29	23 and 28
30	limit 29 to human
31	15 and 30
32	limit 31 to (english or french)

Database: EBSCO CINAHL	
Date of Search:	20 July 2012
Years Searched:	1982 – 20 July 2012
Alerts:	None
Limits:	None
Filters:	Observational study search filter: <i>Scottish Intercollegiate Guidelines Network (SIGN)</i> . "Search Filters." <i>Search Filters</i> . Health Improvement Scotland. 16 Sept. 2011. Web. 21 May 2011. Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	(MH "Prospective Studies")
2	(MH "Case Control Studies+")
3	(MH "Correlational Studies")
4	(MH "Nonconcurrent Prospective Studies")
5	(MH "Cross Sectional Studies")
6	(cohort adj (study or studies)).tw.
7	(observational adj (study or studies)).tw.
8	S1 or S2 or S3 or S4 or S5 or S6 or S7

9	(MH "Alzheimer's Disease")
10	(MH "Risk Factors")
11	"etiology"
12	"prevention and control"
13	"causation"
14	S10 or S11 or S12 or S13
15	(MH "Stress") OR "stress" OR (MH "Stress Disorders, Post-Traumatic") OR (MH "Stress, Occupational") OR (MH "Stress, Psychological")
16	(MH "Anxiety") OR "Anxiety" OR (MH "Anxiety Disorders")
17	S15 or S16
18	S14 and S17
19	S9 and S18
20	S8 and S19

Database: Ovid PsycINFO	
Date of Search:	19 Feb 2013
Years Searched:	1806 – 19 Feb 2013
Alerts:	None
Limits:	Language (English, French) Human subjects
Filters:	Observational study search filter: School of Public Health. "Search Filters for Ovid PsycINFO." <i>Ovid PsycINFO</i> . University of Texas: Health Science Center at Houston. 10 Oct. 2011. Web. Etiology/Risk filter: Lamar Soutter Library. "PsycInfo Evidence-Based Filters." <i>Psychology/Psychiatry Evidence-Based Resources</i> . University of Massachusetts Medical School. 23 Aug. 2006. Web. 21 May 2011.
Search Strategy:	
Line #	Strategy
1	Dementia/ or Alzheimer's Disease/
2	(Alzheimer* or presenile dementia* or acute confusional senile dementia or Senile dementia* or primary senile degenerative dementia or primary degenerative senile).mp.
3	1 or 2
4	etiology.ti.
5	exp PREVENTION/
6	Epidemiolog\$.ti.
7	causal.ti.
8	cohort.ti.
9	emperical.ti.
10	risk.ti.
11	odds.ti.
12	case control.ti.
13	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	((case* adj5 control*) or (case adj3 comparison*) or case-comparison or control group*).ti,ab. not "Literature Review".md.
15	((cohort or longitudinal or prospective or retrospective).ti,ab,id. or longitudinal study.md. or prospective study.md. or retrospective study.md.) not "Literature

	Review".md.
16	14 or 15
17	Psychological Stress/ or Chronic Stress/ or Occupational Stress/ or Acute Stress Disorder/ or Posttraumatic Stress Disorder/ or stress.mp. or Stress/
18	13 and 17
19	3 and 18
20	limit 19 to human
21	16 and 20
22	limit 21 to (english or french)

Database: EBSCO AARP Ageline	
Date of Search:	19 Feb 2013
Years Searched:	1978 – 19 Feb 2013
Alerts:	None
Limits:	None
Filters:	None
Search Strategy:	
Line #	Strategy
1	Alzheimer's Disease OR presenile dementia* OR acute confusional senile dementia OR Senile dementia* OR primary senile degenerative dementia OR primary degenerative senile
2	cohort or longitudinal or prospective or retrospective
3	case control or case comparison
4	etiology or risk factor or causation or prevention and control
5	stress OR post traumatic stress disorder OR psychological stress OR occupational stress
6	S4 AND S5
7	S1 AND S6
8	S2 OR S3
9	S7 AND S8

Database: American Journal of Alzheimer's Disease and Other Dementias (SAGE Journals Online)	
Date of Search:	19 Feb 2013
Years Searched:	1986 – 19 Feb 2013
Alerts:	None
Limits:	None
Filters:	Observational study filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	risk or etiology (in all fields)andstress (in all fields) and not caregiver (in all fields)

Database: International Journal of Alzheimer's Disease	
Date of Search:	19 Feb 2013
Years Searched:	2009 – 19 Feb 2013
Alerts:	None
Limits:	None
Filters:	Observational study filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	No search engine available, therefore, all five volumes of the journal (2009, 2010, 2011, 2012, 2013) were scanned. Articles deemed potentially relevant were imported into DistillerSR.

Database: Google	
Date of Search:	19 Feb 2013
Years Searched:	N/A
Alerts:	None
Limits:	None
Filters:	Observational study filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	"Alzheimer's Disease" OR "presenile dementia" OR "acute confusional senile dementia" OR "Senile dementia" OR "primary senile degenerative dementia" OR "primary degenerative senile" AND "risk" OR "risk factor" OR "etiology" AND "stress" <i>First 10 pages scanned for relevant articles.</i>

Database: GoogleScholar	
Date of Search:	19 Feb 2013
Years Searched:	N/A
Alerts:	None
Limits:	None
Filters:	Observational study filter: None Etiology/Risk filter: None
Search Strategy:	
Line #	Strategy
1	"Alzheimer's Disease" OR "presenile dementia" OR "acute confusional senile dementia" OR "Senile dementia" OR "primary senile degenerative dementia" OR "primary degenerative senile" AND "risk" OR "risk factor" OR "etiology" AND "stress" <i>First 10 pages scanned for relevant articles.</i>

APPENDIX C-2: Newcastle-Ottawa Scale

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

- 1) Is the case definition adequate?
 - a) yes, with independent validation *
 - b) yes, eg record linkage or based on self reports
 - c) no description
- 2) Representativeness of the cases
 - a) consecutive or obviously representative series of cases *
 - b) potential for selection biases or not stated
- 3) Selection of Controls
 - a) community controls *
 - b) hospital controls
 - c) no description
- 4) Definition of Controls
 - a) no history of disease (endpoint) *
 - b) no description of source

Comparability

- 1) Comparability of cases and controls on the basis of the design or analysis
 - a) study controls for _____ (Select the most important factor.) *
 - b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

- 1) Ascertainment of exposure
 - a) secure record (eg surgical records) *
 - b) structured interview where blind to case/control status *
 - c) interview not blinded to case/control status
 - d) written self report or medical record only
 - e) no description
- 2) Same method of ascertainment for cases and controls
 - a) yes *
 - b) no
- 3) Non-Response rate
 - a) same rate for both groups *
 - b) non respondents described
 - c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

- 1) Representativeness of the exposed cohort
 - a) truly representative of the average _____ (describe) in the community ★
 - b) somewhat representative of the average _____ in the community ★
 - c) selected group of users eg nurses, volunteers
 - d) no description of the derivation of the cohort
- 2) Selection of the non exposed cohort
 - a) drawn from the same community as the exposed cohort ★
 - b) drawn from a different source
 - c) no description of the derivation of the non exposed cohort
- 3) Ascertainment of exposure
 - a) secure record (eg surgical records) ★
 - b) structured interview ★
 - c) written self report
 - d) no description
- 4) Demonstration that outcome of interest was not present at start of study
 - a) yes ★
 - b) no

Comparability

- 1) Comparability of cohorts on the basis of the design or analysis
 - a) study controls for _____ (select the most important factor) ★
 - b) study controls for any additional factor ★ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

- 1) Assessment of outcome
 - a) independent blind assessment ★
 - b) record linkage ★
 - c) self report
 - d) no description
- 2) Was follow-up long enough for outcomes to occur
 - a) yes (select an adequate follow up period for outcome of interest) ★
 - b) no
- 3) Adequacy of follow up of cohorts
 - a) complete follow up - all subjects accounted for ★
 - b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ★
 - c) follow up rate < ____ % (select an adequate %) and no description of those lost
 - d) no statement

APPENDIX C-3: Excluded studies (n=22) following full-article screening

Study	Reason for Exclusion
Andel, Ross. "The association between occupational complexity and the risk of dementia: Results from case-control and twin analyses." Dissertation Abstracts International Section A: Humanities and Social Sciences. 64.12-A (2004): 4579.	Did not examine exposure of interest
Chan WC, et al. "Neuropsychiatric symptoms are associated with increased risks of progression to dementia: a 2-year prospective study of 321 Chinese older persons with mild cognitive impairment." Age & Ageing 40.1 (2011): 30-5.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia
Charles E, et al. "[Links between life events, traumatism and dementia; an open study including 565 patients with dementia]." [in French] Encephale 32.5 Pt 1 (2006): 746-52.	Not a case-control/cohort study
Clement J.P., Darhout N. and Nubukpo P.. "Life events, personality and dementia". Psychologie & neuropsychiatrie du vieillissement 1.2 (2003): 129-138.	AD not distinguished from all-cause dementia(relevant quantitative data for AD not provided)
Crowe M, et al. "Do work-related stress and reactivity to stress predict dementia more than 30 years later?." Alzheimer Disease & Associated Disorders 21.3 (2007): 205-9.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia
Crowe, Michael. "Personality and risk of cognitive impairment: A prospective study of Swedish twins." Dissertation Abstracts International Section A: Humanities and Social Sciences. 65.9-A (2005): 3517.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia
Dent, O. F. "Long-term health consequences of wartime imprisonment: A review of the Concord hospital POW project." Australasian Journal on Ageing. 18.3 (1999): 109-113.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia
Fei M, et al. "Prevalence and distribution of cognitive impairment no dementia (CIND) among the aged population and the analysis of socio-demographic characteristics: the community-based cross-sectional study." Alzheimer Disease & Associated Disorders 23.2 (2009): 130-8.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia
French LR, et al. "A case-control study of dementia of the Alzheimer type." American Journal of Epidemiology 121.3 (1985): 414-21.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia
Gallacher J, et al. "Does anxiety affect risk of dementia? Findings from the Caerphilly Prospective Study." Psychosomatic Medicine 71.6 (2009): 659-66.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia
Gallassi R, et al. "Are subjective cognitive complaints a risk factor for dementia?." Neurological Sciences 31.3 (2010): 327-36.	Did not examine exposure of interest
Lupien SJ, et al. "The Douglas Hospital Longitudinal Study of Normal and Pathological Aging: summary of findings." Journal of Psychiatry & Neuroscience	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia

30.5 (2005): 328-34.	
Magri F, et al. "Stress and dementia: the role of the hypothalamic-pituitary-adrenal axis." <i>Aging-Clinical & Experimental Research</i> 18.2 (2006): 167-70.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia
Meins W and Dammast J. "Do personality traits predict the occurrence of Alzheimer's disease?." <i>International Journal of Geriatric Psychiatry</i> 15.2 (2000): 120-4.	Did not provide risk estimates
Nabalamba A and Patten SB. "Prevalence of mental disorders in a Canadian household population with dementia." <i>Canadian Journal of Neurological Sciences</i> 37.2 (2010): 186-94.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia
O'Brien J. "Dementia associated with psychiatric disorders." <i>International Psychogeriatrics</i> 17 Suppl 1.(2005): S207-21.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia
Palmer K, et al. "Predictors of progression from mild cognitive impairment to Alzheimer disease." <i>Neurology</i> 68.19 (2007): 1596-602.	Reported on risk of progression from MCI to AD
Persson, Goran and Skoog, Ingmar. "A prospective population study of psychosocial risk factors for late onset dementia." <i>International Journal of Geriatric Psychiatry</i> . 11.1 (1996): 15-22.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia
Qureshi SU, et al. "Greater prevalence and incidence of dementia in older veterans with posttraumatic stress disorder." <i>Journal of the American Geriatrics Society</i> 58.9 (2010): 1627-33.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia
Ravona-Springer R, Beeri MS and Goldbourt U. "Exposure to the Holocaust and World War II concentration camps during late adolescence and adulthood is not associated with increased risk for dementia at old age." <i>Journal of Alzheimer's Disease</i> 23.4 (2011): 709-16.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia
Stonnington C.M., et al. "Anxiety affects cognition differently in healthy apolipoprotein E 4 homozygotes and non-carriers". <i>Journal of Neuropsychiatry and Clinical Neurosciences</i> 23.3 (2011): 294-299.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia
Wang HX, et al. "Personality and lifestyle in relation to dementia incidence." <i>Neurology</i> 72.3 (2009): 253-9.	AD was not an outcome/AD not diagnosed according to acceptable criteria/AD not distinguished from all-cause dementia

APPENDIX C-4: Included Studies (n=9)

Andel R et al. "Work-related stress may increase the risk of vascular dementia." *Journal of the American Geriatrics Society* 60.1 (2012): 60-7.

Duberstein PR et al. "Personality and risk for Alzheimer's disease in adults 72 years of age and older: a 6-year follow-up." *Psychology & Aging* 26.2 (2011): 351-62.

Johansson L et al. "Midlife psychological stress and risk of dementia: a 35-year longitudinal population study." *Brain* 133 (2010): 2217-24.

Wang HX, et al. "Psychosocial stress at work is associated with increased dementia risk in late life." *Alzheimer's & Dementia* 8.2 (2012): 114-20.

Wilson RS et al. "Chronic psychological distress and risk of Alzheimer's disease in old age." *Neuroepidemiology* 27.3 (2006): 143-53.

Wilson RS et al. "Proneness to psychological distress and risk of Alzheimer disease in a biracial community." *Neurology* 64.2 (2005): 380-2.

Wilson RS et al., "Proneness to psychological distress is associated with risk of Alzheimer's disease." *Neurology* 61.11 (2003): 1479-85.

Wilson RS et al. "Vulnerability to stress, anxiety, and development of dementia in old age." *American Journal of Geriatric Psychiatry* 19.4 (2011): 327-34.

Yaffe K et al. "Posttraumatic stress disorder and risk of dementia among US veterans." *Archives of General Psychiatry* 67.6 (2010): 608-13.