Eye disease and cognition: a Canadian hospital-based cross-sectional study

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Abstract

Much attention is being expended to better understand the causes of cognitive impairment. The purpose of this thesis was to determine whether sensory deprivation, in particular vision loss due to age-related eye disease, is related to cognitive function in older adults, and if so, why. The epidemiological evidence thus far is conflicting and has some limitations such as using cognitive tests that rely on vision or only using a single global cognitive test. This thesis examined the relationship between eye disease and cognition by using several cognitive tests that do not rely on vision and by studying vision loss due to two different eye diseases that are common in old age. Our hypothesis was that people with glaucoma or age-related macular degeneration (AMD) would have worse cognitive function on all six cognitive tests and that these relationships would be explained by their more limited involvement in cognitive activities. This work used baseline data from a 2-year prospective hospital-based cohort study of 235 older adults. We found that older adults with AMD and glaucoma participated in fewer activities at least once per month compared to older adults with normal vision after adjustment for demographic and health variables (β=-4.8, 95% CI= -6.8, -2.8) and (β=-2.6, 95% CI= -4.3, -0.9), respectively. Furthermore, we found that AMD was associated with lower verbal fluency letter scores (β=-2.2, 95% CI= -4.1, -0.3) while glaucoma was related to worse immediate and delayed recall of items on the logical memory story (β=-1.7, 95% CI= -3.1, -0.4) and (β=-1.5, 95% CI= -2.9, -0.1). These associations were all attenuated by the addition of cognitive activities to the models, which may indicate its role as a mediator. Longitudinal studies are needed to provide more rigorous evidence. If confirmed in prospective studies, efforts to improve cognitive activities and cognitive function could be targeted specifically at older adults with vision loss.

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List of abbreviations

Ach	Acetylcholine
AChE	Achetylcholinesterase
AD	Alzheimer's Disease
ADL	Activities of Daily Living
AMD	Age-related Macular Degeneration
BDNF	Brain-Derived Neurotrophic Factors
CAMCOG	Cambridge Cognitive Examination
CFH	Complement Factor H
ChEIs	Acetylcholinesterase inhibitors
CONSORT	Consolidated Standards of Reporting Trials
COSMIC	Cohort Studies of Memory in an International Consortium
DSST	Digit Symbol Substitution Test
DV	Dependent Variable
ETDRS	Early Treatment of Diabetic Retinopathy Study
FC	Functional Connectivity
GDS	Geriatric Depression Scale
IADL	Instrumental Activities of Daily Living
IOP	Intraocular Pressure
IV	Independent Variable
LGN	Lateral geniculate nucleus
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
NMDA receptor	N-methyl-D-aspartate receptor
POAG	Primary Open Angle Glaucoma
RCT	Randomized Controlled Trial
RGC	Retinal ganglion cells
RPE	Retinal pigment epithelial
RNFL	Retinal nerve fiber layer
SD	Standard deviation
VEGF	Vascular Endothelial Growth Factors
VLSA	Victoria Lifestyle Activities Questionnaire

Introduction

Population aging is a universal phenomenon that has been gaining attention in the past few years, with reason. Advances in medicine and public health have increased the lifespan of numerous people and the Baby Boomer generation has begun to reach the age of 65. In fact, population aging is becoming a growing interest in Canada and there has been a noticeable spike in the number of people aged 85 or above[1]. According to the 2016 Statistics Canada Census, 13% of Canadians are aged 65 and above, and 2% of Canadians (770 780) are 85 or older, a number that is seven times higher than it was 50 years ago[1]. In Canada, the proportion of adults aged 65 or older is projected to increase to 22.6% by 2041[2]. Needless to say, there is a shift occurring in population trends, which means that there is a growing need for research focusing on older adults.

An important and well-known aspect of aging is a decline in memory and cognition, which can vary from one older adult to another but is typically an integral part of aging[3, 4]. Research suggests that the greatest risk factor for cognitive decline is age[5]. In fact, there is evidence of reduced coordinated activity in the brain and less localized neural activity in the aging brain even with no disease[5]. Although some cognitive decline seems to be a normal trajectory for the aging brain, mild cognitive impairment occurs when the cognitive functioning of the brain deteriorates beyond normal trajectory for the aging brain, but does not yet meet criteria for neurodegenerative disorders such as dementia[5, 6]. Established risk factors for mild cognitive impairment include: hypertension, diabetes, cerebrovascular disease, diet, age, and prior cognitive impairment[5, 7, 8]. The focus of this research is to investigate whether age-related eye disease, which is common in older age, is associated with cognitive function. Previous cross-sectional and prospective studies

demonstrate associations between sensory system losses (i.e., hearing, vision, and olfactory loss) and risk of cognitive impairment[9-14]. In terms of vision loss, there has been research specifically assessing eye disease and cognition[12, 15-19]. However, since the research for vision loss and cognitive impairment is limited and conflicting, there is uncertainty about whether eye disease is a risk factor for cognitive impairment.

The overall objective of this research was to examine the relationship between eye disease and cognition in older adults. Four specific research questions were addressed: 1) Do older adults with glaucoma or AMD participate in fewer cognitive activities per month compared to older adults without one of these eye diseases? 2) Are the reductions in activities in those with AMD or glaucoma due solely to specific subtypes of activities? 3) Do older adults with glaucoma or AMD experience worse cognitive function compared to older adults without one of these eye diseases? 4) Does reduced monthly participation in cognitive activities mediate the association between eye disease and cognition?

Age-related macular degeneration and glaucoma were chosen for this study because they are common eye diseases and they affect different types of visual function; AMD primarily causes loss of visual acuity or central vision, whereas glaucoma initially causes loss of visual field or peripheral vision, which can lead to complete blindness if untreated.

This research is clinically significant for a few reasons. Firstly, this study will be the first to try and explain why eye disease and cognition are related by examining cognitive activities as a mediator. Secondly, participation in cognitive activities is potentially modifiable if research provides evidence that it does act as a mediator. Lastly, the findings from this project might

encourage scientists and low vision rehabilitation centres to develop cognitive interventions targeted specifically for adults with poor vision thus providing them with the necessary cognitive training to hopefully suppress cognitive decline. Correspondingly, these findings might encourage ophthalmologists, low vision rehabilitation centres and senior home management to promote engagement in a variety of cognitive activities, which may promote successful aging.

This manuscript-based thesis is organized with the first introductory section reviewing the current literature, followed by the conceptual framework for the study, the research questions that were addressed, an overview of the methodology, and analyses, the first manuscript, the second manuscript, as well as an overall discussion and conclusion. The literature review will focus on the current literature surrounding cognitive impairment, age-related macular degeneration, glaucoma, the relationship between eye disease and cognition, the relationship between eye disease and cognitive activities, as well as the association between cognitive activities and cognition. The methodology and analysis sections will elaborate on important methodological/analytical aspects that were not explained in detail in the manuscripts. Finally, the discussion and conclusion sections will tie together both manuscripts in a cohesive and coherent manner. The results of both manuscripts will be interpreted and expanded in these sections, and implications of the findings will be discussed.

Chapter 1: Cognitive Impairment

1.1.1 What is cognitive impairment?

Due to the broad and complex nature of the condition, defining cognitive impairment has been challenging[20]. Published literature utilizes various diagnostic criteria, terms and approaches to

define mild cognitive impairment (MCI)[20], but generally it is defined as a common condition of aging with memory and attention loss symptoms[21, 22]. Cognitive impairment can occur in various degrees that can be problematic ranging from mild cognitive impairment to severe dementia[21-23]. I will focus most of Chapter 1 on mild cognitive impairment or on cognitive function in those without dementia because the focus of this project is on understanding factors associated with the earlier phase of cognitive decline rather than dementia.

The brain is a highly complex and vital organ that is constantly developing and changing throughout the years. Although there are some structural, neuronal, and functional brain changes that are expected with aging, there are some that might play a role in cognitive impairment[21, 24]. Research suggests hippocampal and cerebral atrophy[25], increased oxidative stress, neuroinflammation, altered cellular signalling and gene expression, decreases in synaptic neuroplasticity and neurogenesis as related to cognitive impairment[21]. There are many other types of risk factors also associated with cognitive impairment[26]. A clinical review highlighted age, male sex, lower education, vascular diseases (diabetes and hypertension), Apolipoprotein E ε4 genotype, vitamin D deficiency, prior clinical illness, depression, and certain medications (i.e., anticholinergics, opiates, benzodiazepines, antihistamines, tricyclic anti-depressants, etc), as potential risk factors[26]. Other suggested risk factors include HIV, syphilis, infection, renal failure, glycemia and impairment in instrumental activities of daily living[3, 26]. Clearly, cognitive impairment appears to be a multifactorial condition, which adds to the complexity of its study.

1.1.2 Measurement of cognitive impairment

Being able to identify and precisely measure the degree of a condition is key to understanding aetiology and finding treatments. One common way to assess cognitive impairment is with neuropsychological tests. Since cognition encompasses a variety of domains (memory, attention, visual spatial, processing speed, reasoning, etc), there are many neuropsychological scales that can be used to measure the various executive function tasks[27]. A systematic review and meta-analysis assessing different screening measures for cognitive impairment and dementia identified 11 neuropsychological tests that are used to measure MCI[27]. Another research group evaluated three commonly used cognitive impairment scales (Mini Mental State Examination (MMSE), Alzheimer Disease Assessment Scale (ADAS-Cog), and the Cambridge Cognitive Examination (CAMCOG). They concluded that all three tests reflect a valid common dimension of cognitive impairment, and the results from these scales are comparable[28]. Essentially, although there are different scales that are used in clinical and research settings to measure cognitive impairment, the results of some of the most common scales are comparable to one another, which is ideal in research.

One important aspect to note is that most of these tests are visual, which is problematic for vision-impaired individuals[29]. An easy solution would be to not test vision-impaired people on the visual components of the tests; however missing values in cognitive tests can affect the validity of the test and can make the results difficult to interpret[29]. Furthermore, since vision impairment is highly prevalent in older adults it would be beneficial to have measures tailored to this population. For these reasons, an adaptation of the Mini-Mental State Examination scale (MMSE-Blind) omitting 8 items requiring good vision has been created and validated[29, 30].

1.1.3 Frequency of cognitive impairment

The prevalence of cognitive impairment in adults without dementia is considerable and increases with age[31]. In 2001-2005, the prevalence of adults aged 71-79 years in the US was 16.0% (95% CI=11.5, 20.5)[31]. The prevalence was higher for US adults aged 80-89 years (29.2, 95% CI= 24.3, 34.1) and even higher for those aged 90 or above (39.0, 95% CI=25.7, 52.2)[31]. Consistent with the US, the prevalence of cognitive impairment in adults without dementia also increases with age in a Canadian population[32]. In 1997, the prevalence of cognitive impairment in Canadian adults aged 65-74 years was 11.0% (95% CI= 9.0, 13.0)[32]. That prevalence increased to 24.0% (95% CI= 21.7–26.3) for Canadian adults aged 75-84, and increased to 30.3% (95% CI= 27.0–33.6) for those aged 85 years or more[32]. Cognitive impairment is most frequently seen in dementia disorders and the prevalence of dementia increase with age[33]. The prevalence also varies by sex. Based on a meta-analysis, from ages 60-79 the prevalence is higher among men, but from ages 80 onwards, the prevalence is higher in women[33]. In 2013, the prevalence of dementia standardized for sex and age in the US was 6.77%[33].

Published research also indicates a fairly high prevalence rate of mild cognitive impairment[20]. Definitions and criteria for cognitive impairment have changed over time and have lacked consensus leading to wide variability in published prevalence and incidence rates of mild cognitive impairment[20]. In 2012, Ward and associates conducted a systematic search of 42 international publications and found that prevalence estimates and incidence rates were quite variable[20]. Prevalence of mild cognitive impairment ranged from 3% to 42%, while the incidence rate ranged from 21.5-71.3 per 1000 person years[20]. These wide ranges hinder our ability to get

an accurate picture of the burden of cognitive impairment. From this stemmed the Cohort Studies of Memory in an International Consortium (COSMIC collaboration), which is a collaboration that brings together international data from cohort studies[34]. The researchers conducted an analysis of 11 longitudinal population-based studies of cognitive aging by harmonizing and pooling the raw data[34]. Based on a set of rigorous pre-defined criteria for cognitive impairment, they identified an overall crude prevalence of MCI of 5.9% (5.5-6.3), but also demonstrated that this prevalence increased with age; 4.5% prevalence for ages 60-69, 5.8% prevalence for ages 70-79, and 7.1% prevalence for people aged 80-89[34]. Close to 44 million people worldwide suffer from mild cognitive impairment[35] and 758 million people worldwide suffer from dementia[33]. These numbers are worrisome, especially considering the care needs of people with mild cognitive impairment and dementia, as well as the possible association between cognitive impairment and mortality[36].

1.1.4 Economic consequences of cognitive impairment

Understanding the economic consequences of a clinical condition allows healthcare practitioners, governments, and organizations to make well-informed decisions about the course of action regarding new treatments and therapies[37]. Economic data could also potentially shape management strategies and help identify individuals who would benefit the most from interventions, treatments and preventative measures[37]. However, as was previously highlighted, one recurring problem in the literature has been universally defining cognitive impairment[20], which might be a reason why to date there are little economic data available[37]. Established economic research on Alzheimer's disease (AD) depicts that individuals with the disease have much higher health care costs than individuals without the disease[37]. Interestingly, it seems that

the costs most associated with AD are indirect costs with regards to caregivers (i.e., unpaid caregiver time, lost caregiver productivity)[37]. Although there is very limited economic research for mild cognitive impairment, a recent US cross-sectional study did an analysis of the financial burden and healthcare utilization of older adults with various stages of cognitive impairment (amnestic mild cognitive impairment, mild dementia, moderate dementia, and severe dementia)[35]. They were interested in comparing direct medical spending, which consists of medical costs covered by insurance in the past 2 years such as hospitalizations, nursing homes, doctor visits, outpatient surgery, prescription drugs, and home health care[35]. Compared to individuals with normal cognition, individuals with severe dementia, moderate dementia, and mild dementia spent more ($113,318, $40,122, and $64,663, respectively)[35]. Further regression analyses adjusting for age, gender, race, education, marital status, and residential region indicated that the odds of hospitalizations, use of nursing homes, and use of home care services were 1.42 (95% CI= 1.11, 1.81), 2.28 (95% CI= 1.64, 3.17) and 1.39 (95% CI= 0.96, 2.01) times higher in individuals with poorer cognitive states[35]. These results provide an idea of the economic consequences of cognitive impairment; however future studies and possibly a health economic evaluation are needed to solidify these findings. In sum, there is a gap in the literature with regards to the economic consequences of cognitive impairment. Findings from a recent US cross-sectional study depict increasing medical costs with poorer cognitive states[35], but future economic studies are warranted to better steer and guide decision-making.

1.1.5 Disability consequences of cognitive impairment

According to the World Health Organization (WHO), a disability is “an umbrella term referring to impairments, activity and participation limitations”[38]. There is consistent epidemiological

evidence suggesting that cognitive impairment might be one of the leading causes of functional disability (activities of daily living (ADL), instrumental activities of daily living (IADL), mobility)[39-50]. Due to the large number of studies assessing cognitive impairment and disabilities, Lindbergh and colleagues conducted a systematic review and meta-analysis of the available data[44]. They found that individuals with mild cognitive impairment displayed significantly greater difficulties in instrumental activities of daily living compared to those without MCI (Hedges g score= 0.76)[44]. Their mean Hedges g score (measure of effect size) depicts the large magnitude in the difference in disability in those with MCI and without MCI[44]. Clinical research also suggests that the odds of functional disability were 16.0 (95% CI= 10.8, 23.6) times higher in hospitalized older adults who experienced cognitive decline compared to hospitalized older adults who did not experience cognitive decline[46]. Furthermore, it seems that cognition is predictive of having difficulty with IADL tasks such as managing money, using the telephone, making meals, going grocery shopping, and light housework, but not of ADL tasks such as bathing, dressing, and eating[47]. It was posited that brief cognitive measures were more predictive of IADL activities than ADL activities because IADL limitations typically develop before ADL limitations[47].

Another disability that has been linked to cognitive impairment is mobility and the risk of falling in older adults[48-50]. Analyses depict that community-dwelling older adults with MCI perform far worse than community-dwelling older adults without MCI on a variety of mobility measures namely habitual gait speed (walk straight for 4 m), Short Physical Performance Battery (standing balance, walking speed, standing from a chair), basic lower extremity function and advanced lower extremity function[49]. Findings from a prospective longitudinal study of 102 people without dementia indicate that older adults with baseline mild cognitive impairment were 4.8 (95% CI=

1.3, 18.2) times more likely to fall than older adults with no baseline cognitive impairment, thus supporting the association between cognitive impairment and falling[48]. This OR was adjusted for prior falls and for Parkinson's disease[48]. Lastly, a recent cross-sectional study of 327 community dwelling adults suggests that the likelihood of poorer cognitive scores rises with increased mobility difficulties, which represents a dose-response pattern[50]. Cognition was measured with the Montreal Cognitive Assessment (MoCA), which is an overall score out of 30 assessing different aspects of cognition such as visuospatial skills, executive functioning, memory and attention[50]. The exposure variable was measured using a series of mini physical tests (e.g., picking up a penny). The final mobility variable included four categories: 1) no mobility dysfunction, 2) upper extremity impairment, 3) lower extremity impairment, and 4) mobility limitation. They found that the upper extremity impairment group, the lower extremity impairment group, and the mobility limitation group (both upper and lower extremities) had an overall cognitive score that was 1.43 points lower ($p=0.175$), 2.95 points lower ($p<0.001$), and 3.78 points lower ($p<0.001$) compared to the mobility dysfunction group[50]. The authors stipulated that these results support a dose-response pattern since cognitive performance scores differ based on participants mobility dysfunction stage[50]. Overall, the evidence points towards functional disability and mobility as consequences associated with cognitive impairment, which negatively impacts everyday functioning. Additionally, early stages of cognitive impairment might first affect tasks requiring greater executive functioning (e.g., grocery shopping, and managing money)[47]. Disability in higher order tasks might not be as noticeable to healthcare providers, thus placing more responsibility and necessary awareness on the individuals having this condition or their caregivers. Given the profound implications on healthcare costs and disability, prevention strategies are needed.

1.2 Prevention of cognitive impairment

Cognitive impairment is a daunting and disheartening illness, which can leave those affected and their caregivers feeling mentally, physically, and emotionally drained. Furthermore, as it is considered a growing public health concern, there is a definite need to identify effective prevention strategies[51]. Many adults fear aging because of the potential loss in their cognitive abilities and try to find strategies to reduce their risk often by turning to their doctors[52, 53]. Findings from an annual physician survey in the US state that 40% of 1,880 physicians who completed the survey report discussing concerns related to cognitive impairment with older adults[53]. These physicians recommended healthy diet, physical activity, and mental stimulation as preventative measures[53]. Below is an overview of the current evidence regarding these three modifiable behaviours.

1.2.1 Diet

Existing observational studies seem to indicate a relationship between healthy diet such as the Mediterranean style diet and cognition[54-56]. The Mediterranean style diet (MeDi) consists of a diet rich in plant foods (vegetables, fruit), grains, fish, and wine[55, 56] and it has been shown to decrease the risk of some cancers[57, 58], all-cause mortality[59, 60], and heart disease[61]. Since dietary modification is a relatively easy preventative measure to incorporate in the everyday routine, it is worthwhile to know if there are cognitive benefits[55, 56]. A prospective cohort study followed 3,790 community-dwelling older adults for close to 8 years and conducted mixed model analyses to examine adherence to Mediterranean diet and cognitive scores[56]. After adjusting for age, sex, race, education, participation in cognitive activities, total energy intake, and interaction between time and diet quality score, they found that higher Mediterranean diet scores were associated

with higher baseline cognitive scores (β =0.0070, p<0.001), and with slower cognitive decline (β =0.0014 per 1-point increase, p<0.001)[56]. These results depict that individuals who have greater MeDi adherence scores demonstrated slower cognitive decline over time compared to individuals with lower MeDi adherence scores[56]. Similarly, a retrospective cohort study of 352 older adults support lifetime dietary pattern (from childhood to middle age) recall as a predictor of cognitive performance in community-dwelling older adults[55]. Lastly, to further strengthen the evidence, results from a systematic review strongly support the effect of the MeDi on global cognition, thus making the Mediterranean diet a possibly viable preventative option for cognitive impairment[54]. No randomized controlled trials, however, have yet been done.

1.2.2 Physical activity

A second modifiable lifestyle behaviour consists of physical activity, which is thought to have substantial benefits on many aspects of one's health such as reduced risk of chronic diseases (i.e., cardiovascular disease, diabetes, some type of cancers), reduced chronic inflammation, obesity, depression, hypertension, mortality, osteoporosis, and quality of life[62-64]. It therefore seems as though there are considerable advantages associated with physical activity. Considering the apparent widespread health benefits of physical activity, it would make sense to see whether this can prevent or reduce the risk of cognitive impairment. There is some epidemiological evidence showing a decreased risk of incident cognitive impairment in those who are more physically active[51, 65]. A large prospective cohort study following 3903 older adults for 2 years determined that moderate or high levels of physical activity are associated with reduced odds of incident cognitive impairment for older adults with functional impairment at baseline ($OR_{moderate}$= 0.57, p=0.01, OR_{high}= 0.54, p<0.01)[51]. Further analyses also determined that moderate or high levels of

physical activity are associated with a reduced risk of incident cognitive impairment for older adults without functional impairment at baseline ($OR_{moderate}$=0.44, p=0.01, OR_{high}= 0.46, p=0.01)[51]. Other studies have found similar results[66, 67]. An RCT of 170 older adults at risk for Alzheimer's disease found a small difference in cognitive scores between the physical activity arm and education arm of the trial[67]. Adults randomized to the education and usual care group scored 1.3 points lower on the ADAS-Cog scale (95% CI= -2.38, -0.22) compared to adults randomized to the physical activity group[67]. Findings from an RCT of 1,635 community-dwelling sedentary adults followed from 2010-2011 contradict the above studies[68]. Older adults in this trial were assigned to the intervention arm (structured physical activity program) or to the control arm (health education workshops) and were followed for two years[68]. Cognitive function was assessed using the Digit Symbol Coding (DSC), which is a test from the Weschler Adult Intelligence Scale and a word-list delayed recall task[68]. After two years, there were no differences in mean DSC scores between the activity intervention group and education group, or any difference in the word-list delayed recall mean scores[68]. Additionally, the odds of MCI or dementia were not statistically significantly higher in the education group (OR=1.08, 95% CI= 0.80, 1.46)[68]. A systematic review and meta-analysis found some benefit of resistance training compared to stretching on reasoning ($p<0.005$), and also found some benefit of Tai Chi compared to no exercise on attention and processing speed ($p<0.001$)[69]. Hence, the evidence for the benefit of physical activity on cognition in older adults is conflicting. Part of the reason for these conflicting findings might be due to the different measurements of physical activity and cognition[69]. Future studies should attempt to use definite and rigorous guidelines to better assess the effect of physical activity on cognitive decline[69].

1.2.3 Cognitive training/Mental stimulation

One last behavioural recommendation that could reduce or prevent the risk of cognitive impairment is cognitive training/mental stimulation[70]. Cognitive training programs focus on the practice of specific cognitive tasks, whereas mental stimulation exercises focus on the practice of cognitively stimulating activities in daily life (e.g., playing chess, reading, crossword puzzles)[70]. In 2013, Reijnders and colleagues conducted a systematic review inclusive of 20 randomized controlled trials (RCTs) that used objective memory performance as their outcome[70]. Of the 20 RCTs, 17 found that memory performance was improved after a memory training intervention[70]. Improvements were found more specifically in tasks related to self-paced memory, working memory, recognition, face-name learning, immediate memory, word list recall, name recall, and story recall[70]. A second systematic review of 31 RCTs was conducted a year later and included a meta-analysis of 3 to 7 RCTs[69]. This meta-analysis demonstrated that those who received cognitive training performed better on certain tasks such as the face-name recall ($Z=2.35$, $p=0.02$), immediate recall ($Z=2.52$, $p=0.02$), paired associates ($Z=3.22$, $p=0.001$) and subjective measures of cognitive performance ($Z=2.54$, $p=0.01$) compared to controls who did not receive any cognitive training[69]. Conversely, they did not find any differences in performance in the groups for cognitive tasks such as working memory ($Z=1.27$, $p=0.20$), delayed recall ($Z=1.64$, $p=0.10$) or recognition ($Z=1.06$, $p=0.29$)[69]. Although the evidence suggests that cognitive training and mental stimulation are not associated with better performance on all cognitive-related tasks, they have demonstrated improvement on some tasks, which may be beneficial to the prevention of overall cognitive decline[69, 70].

In sum, these three modifiable health behaviours show promise in their ability to prevent cognitive decline but more high quality RCT research is needed to better understand the expected

benefits of these interventions and the mechanisms by which they may work. Proposed biological mechanisms linking the MeDi diet to cognition include vascular dementia, oxidative stress (MeDi diet food elements increase antioxidant enzymes) and inflammation (MeDi diet food elements reduce interleukin cytokines and white blood cells)[71]. A proposed biological mechanism linking both physical activity and cognitive training to cognition is neuroplasticity and training the ability to switch between cognitive tasks to engage different neurobiological pathways[72, 73]. Similar to the MeDi diet, physical activity has also been shown to decrease chronic inflammation via the interleukin-6 cytokine system[62]. Despite the absence of gold standard evidence, health-care practitioners may continue promoting healthy diet, physical activity, and cognitive training/mental stimulation to older adults, as they provide benefits to other chronic conditions as well[57-64].

1.3 Treatment of cognitive impairment

As has been highlighted, cognitive impairment poses an economic and disabling burden, and its prevalence increases with age. It is thus necessary to develop and provide effective treatments to mitigate the consequences associated with cognitive decline. Currently, there are two types of established treatments for cognitive impairment: pharmacologic and non-pharmacologic[74].

1.3.1 Pharmacologic treatments for cognitive impairment

Most pharmacologic treatments for cognitive impairment as a result of dementia focus on acetylcholinesterase inhibitors (ChEIs)[75]. Acetylcholine (Ach) is a neurotransmitter present in organs, autonomic ganglia and in the central nervous system[75]. Acetylcholinesterase (AChE) is an enzyme that catalyzes the Ach neurotransmitter ensuring it goes to a resting state[75]. Hence,

AChE inhibitors have the role of stopping the enzyme from catalyzing the neurotransmitter, allowing the activation to last longer[75]. Since Alzheimer's disease is associated with decreased cholinergic neurons in the brain, these inhibitors are often used to treat symptoms of Alzheimer's disease such as memory loss. The most commonly used AChE inhibitors for cognition are donepezil, rivastigmine and galantamine[75]. Based on the body of evidence, there are conflicting results for cholinesterase inhibitors as treatments for MCI[76]. This variability might in part be due to the complexity surrounding the measurement and definition of cognitive impairment since many of these trials used different ways of measuring cognition[76]. Additionally, a systematic review published in 2013 found that cholinesterase inhibitors did not prevent the progression from MCI to dementia[74]. The authors of this systematic review confirmed that as per the National Institute of Clinical Excellent (NICE) guidelines, cholinesterase inhibitors should not be prescribed clinically to individuals with MCI[74, 77]. Acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) should only be prescribed to individuals with moderate AD severity (MMSE score ranging from 10-20)[77].

Not all pharmacologic treatments target AChE. Memantine is a type of pharmacologic treatment that binds to open NMDA receptors and blocks the influx of glutamate that can damage or kill nerve cells (excitotoxicity) and consequently neuronal dysfunction[78]. Although memantine monotherapy has been linked to minor improvements in cognitive function scores, activities of daily living scores, global functioning assessment scores and stages of dementia assessment scores, the clinical benefit is questioned due to small effect sizes[78].

Nicotine is also a possible pharmacologic treatment for cognitive impairment through its stimulating properties on nicotinic acetylcholine receptors in the central nervous system (CNS)[79,

[80]. It has been proposed that cognitive function is improved with nicotine as a result of enhancement of synaptic plasticity in the cortex, upregulation of growth factors (more specifically brain-derived neurotrophic factors (BDNF)), enhancement of alertness, as well as heightened release of neurotransmitters such as dopamine, serotonin and norepinephrine[80]. Findings from a clinical trial of adults aged 55 or above with MCI indicate that 15mg of nicotine treatment administered with a transdermal patch improved cognitive performance (greater hit reaction time, greater immediate recall, trend of improvements in Digit Symbol Substitution Task)[79]. However, it should also be noted that high doses of nicotine can generate cognitive and behavioural impairments, as well as dependence[80]. Nicotine dependence is heavily influenced by the route of administration[80]. In fact, inhaling nicotine is deemed risky since it is the fastest route to the brain, which can increase the risk of addiction[80]. It is thus stipulated that although many clinical and animal studies demonstrate improvements in cognition due to nicotine treatment, the administration route and quantity should be controlled rigorously[80]. For nicotine therapy, it seems that there is a fine line between therapeutic effects on cognition and long-term adverse consequences such as nicotine addiction[80].

In sum, most of the pharmacological evidence is conflicting, and to date there is no standard of care pharmacological treatment for cognitive impairment[74]. Moreover, AChE inhibitors and memantine are only efficacious for treating moderate AD symptoms but are not recommended for treating MCI[74, 81]. These pharmacological treatments do not stop disease progression[75, 78-81]. Lastly, although nicotine did improve cognitive performance for individuals with MCI, there are also adverse events that make this treatment risky[79, 80]. Further research is necessary to ensure reproducibility and to better assess the long-term effects of these treatments[74].

1.3.2 Non-pharmacologic treatment of cognitive impairment

A systematic review identified three different non-pharmacologic treatments targeted towards people with MCI in AD, as well as the limitations of these interventions[82]. The three non-pharmacologic treatments include physical activity interventions, cognitive interventions, and social interventions[82]. The physical activity interventions received the highest CONSORT mean score (Consolidated Standards of Reporting Trials), and the cognitive interventions scored lowest[82]. Higher mean CONSORT scores indicate clinical trials that better meet the standards of reporting[83]. Some physical activity interventions seem to benefit executive function (but not memory), whereas other physical activity interventions seem to benefit memory (but not executive function)[82]. A second systematic review study also demonstrated mixed results between physical activity (aerobic exercise, resistance training, balance, and control) and cognitive outcomes[74].

Conflicting results were also present in cognitive intervention trials[82]. Furthermore, the authors of this systematic review noted the lack of clarity among intervention studies and raised questions regarding the effectiveness of these interventions after controlling for confounders and whether certain cognitive interventions were more effective than others[82]. These findings are in line with studies mentioned on pages 14-15 (see Section 1.2.3) that found that cognitive interventions seemed to benefit certain cognitive related tasks, while being unbeneficial to others[69, 70]. It might simply be that different interventions stimulate different parts of cognition, which makes it difficult to assess its global impact. Additionally, because cognition is not clear-cut and easy to measure, it is not surprising that the evidence is muddled.

In terms of the effects of social support, one clinical trial was included in the review and social interventions was associated with significant improvement in cognitive and mental function in a sample of 235 adults aged 75 or older[82, 84]. The participants were assessed at baseline and three months after the social intervention[84]. Participants were divided into one of three activity groups (therapeutic writing, exercise, art) based on their interests[84]. In each of the three activity groups, participants were then randomized to the intervention or control group[84]. In total there were three intervention groups and three control groups[84]. The intervention included two trained group leaders that strived to enhance peer support, empowerment, and friendships, along with weekly group meetings for three months[84]. Each group meeting lasted for about six hours[84]. The control group did not have scheduled group meetings with group leaders but could participate in their activities[84]. Cognition was measured with the ADAS-Cog questionnaire, and lower scores indicated greater cognitive functioning[84]. The investigators measured cognitive change by comparing the ADAS-Cog mean scores at baseline and again three months after between the intervention and control groups[84]. Mann-Whitney U tests or t-tests were used to determine statistical significance[84]. After three months, the ADAS-Cog mean score change was highest in the intervention group, with an overall one-point difference[84]. The ADAS-Cog mean scores were 2.6 points lower (95% CI= -3.4, -1.8) for the intervention group, whereas the mean scores were 1.6 points lower (95% CI= -2.2, -1.1) for the control group[84]. This RCT does provide some support for the benefit of social interventions on cognition. Other RCTs with larger sample sizes are needed to confirm these findings.

Accurately measuring the impact of non-pharmaceutical treatments on cognition is quite complex and requires the acknowledgement of various limitations such as: small sample sizes, short intervention periods with limited or short follow-up, variability within interventions

(content, duration, frequency, setting), and failure to account for confounding factors (comorbidities, lifestyle factors, etc)[82]. Based on this systematic review, it can be concluded that non-pharmacologic interventions targeting physical activity, cognitive stimulation and socialization can potentially be used to treat cognitive impairment, but future RCTs accounting for the limitations are needed for more valid results[82].

To sum up, the non-pharmacologic treatments of cognitive impairment mirror the protective factors of cognitive impairment. The evidence seems promising, and in general physical activity, cognitive stimulation, diet, and socialization are good behaviours to adopt for successful aging. Although non-pharmacologic evidence has its limitations, it appears to be less compromising and potentially less harmful compared to the current pharmacological evidence for people with MCI[74, 80]. In conclusion, based on the available treatments (both pharmacologic and non-pharmacologic), there is no standard of care therapy for mild cognitive impairment.

Chapter 2: Relationship between eye disease and cognition

This thesis will look at the relationship between two common age-related eye diseases and cognition. The two eye diseases are age-related macular degeneration and glaucoma. This chapter will describe these diseases in more detail.

2.1 Age-related macular degeneration (AMD)

Age-related macular degeneration (AMD) is a neurodegenerative retinal eye disease with drusen deposits in the macula that affects approximately 1.4 million Canadians[85, 86]. The progression of this disease can be characterized in three stages namely: early, intermediate, and late[85]. The late

stage is the most severe in terms of vision loss and there are two different types of AMD that can be diagnosed: wet (neovascular) or dry AMD[85]. Although dry AMD is more common, neovascular AMD is more debilitating and accounts for over 80% of severe vision loss[85]. According to a meta-analysis, increasing age is one of the top risk factors associated with the disease[87], and considering the aging Canadian population, the amount of people affected by AMD is projected to significantly increase in the next few years[86].

2.1.1 Prevalence

AMD is a global health concern that affects people in many parts of the world[88]. Based on results from a meta-analysis, it is estimated that the global prevalence of any AMD (early or late) is 8.69% (95% CI=4.26-17.40), that the global prevalence of early AMD is 8.01% (95% CI= 3.95-15.49), and that the global prevalence of late AMD is 0.37% (95% CI= 0.18-0.77)[88]. This global prevalence varies slightly based on ethnicity with people of Asian and African ancestry having lower global prevalence rates for any AMD (7.38%, 95% CI= 3.40-14.16 and 7.53%, 95% CI= 3.80-14.89, respectively) compared to people of Hispanic (10.43%, 95% CI= 5.27-20.01) or European ancestry (12.33%, 95% CI= 6.46-22.75)[88]. The number of people with AMD is expected to increase worldwide with projected global cases of any AMD going from 196 million in 2020 to 288 million in 2040[88]. Furthermore, based on this systematic review and meta-analysis, the projected cases are highest in Asia (113 million in 2040), followed by Europe (69 million in 2040), Africa (39 million in 2040), Latin America and Caribbean (39 million in 2040), North America (25 million in 2040) and Oceania (2 million in 2040)[88]. Overall the global prevalence of AMD is 8.69% and is projected to increase globally in the new few years[88].

Identifying its risk factors is key as it may help with disease prevention and early diagnosis and treatment.

2.1.2 Established risk factors

Among the published literature, there are quite a few studies that highlight established risk factors related to AMD[89-94]. The Blue Mountains Eye Study is a large population-based study of vision and eye disease among Australian adults aged 49 and older[89]. Findings from this 15-year follow-up study of 1149 adults show that women are at increased risk for any type of AMD, and that age is associated with increased incidence of both early and late AMD[89]. Additional risk factors identified for both early and late AMD are current smoking, complement factor H gene (C risk allele), and age-related maculopathy susceptibility gene 2 (T risk allele)[89]. The odds of late AMD were 52% lower among those reporting consuming more than one serving of fish per week (OR=0.48, 95% CI=0.29, 0.79)[89]. A different study demonstrated that after adjusting for age, smoking and systolic blood pressure, the odds of AMD in women were 54% lower among women who were active for at least one hour weekly (OR=0.46, 95% CI=0.23, 0.92)[94]. The Epidemiology of Hearing Loss Study indicated that hearing loss and higher density lipoprotein cholesterol were statistically significantly associated with early AMD[90]. Results from a prospective clinic-based study, a whole genome case-control study, and other population-based studies also found that age, smoking, hypertension, complement factor H polymorphism, and sex were risk factors of AMD[91-93]. People who are overweight, obese or with high blood pressure have higher odds of AMD[94]. Cataract surgery is also a risk factor for AMD[87]. Lastly, an epidemiological study examined the prevalence and 15-year incidence rate of AMD associated with the combined influence of four lifestyle behaviours (little physical activity, poor diet,

smoking, and alcohol intake)[95]. After adjustment, the odds of AMD were 5.14 times higher (95% CI= 1.04, 25.45) in individuals who engaged in all four of these behaviours compared to those who did not[95]. These modifiable behaviours are associated with mechanisms such as inflammation, increased oxidative stress, and higher blood lipid levels, which are thought to promote AMD[95]. Based on this evidence, it seems that the odds of AMD are higher with combined risk factors[95].

2.1.3 Treatment

The current standard of care treatment for wet AMD is anti-vascular endothelial growth factor (anti-VEGF) therapy[96]. Research has identified a consistent association between over-expression of VEGF and the creation of new blood vessels in the eye (choroidal neovascularization)[97]. In the past few years, treatments targeting VEGF have been used to improve visual outcomes of people with wet AMD[98, 99]. Studies have been done with a variety of drugs that are injected into the eye to reduce the expression of VEGF (e.g., Ranibizumab, Bevacizumab and Aflibercept)[100, 101]. A single intravitreal dose of anti-VEGF drugs can reduce the expression of VEGF on choroidal neovascularization for up to 4-6 weeks, which is short-term[98]. This means that patients must frequently visit their ophthalmologist for more doses/treatment, which can be both time-consuming, challenging and leaves room for resistance to treatment[98]. Even though anti-VEGF injections are the current "standard of care" treatment for neovascular age-related macular degeneration, researchers are investigating better ways of delivering the drug such as single injection sustained-release implants[98].

In short, the current standard of care for wet AMD is anti-VEGF therapy. However, because it requires frequent injections, researchers and clinicians are turning towards other options to see whether the effectiveness of the outcome is superior, and whether the frequency of treatment is lower[98]. However, for the moment, there is no therapy that has consistently been identified as superior to the standard of care.

To summarize, AMD is a neurodegenerative retinal eye disorder[85] primarily impairing central vision with a global prevalence close to 9%[88]. Previous cataract surgery, older age, sex, smoking, hypertension, C and T risk alleles, high blood pressure and BMI are some established risk factors[87, 89-94]. Currently, the standard treatment for AMD is anti-VEGF therapy[98].

2.2 Glaucoma

Glaucoma defines a group of diseases/conditions that share the mutual symptom of optic nerve degeneration, which can cause impairment to the visual field[102]. The most common form of glaucoma is primary open-angle (POAG). The cause of POAG is unknown but a major risk factor and the sole treatment target is increased eye pressure[102,103]. It is estimated that over 400,000 Canadians have glaucoma[104]. However, glaucoma is primarily asymptomatic and therefore many people are unaware of their condition and this estimate could under-represent the actual number of glaucoma cases in Canada[103]. Similarly to AMD, glaucoma is strongly related to age[104]. Thus, the amount of people living with glaucoma is also projected to significantly increase in the next few years[105].

2.2.1 Prevalence

Like AMD, glaucoma is also a global health concern and a leading cause of irreversible blindness[106]. Global estimates of prevalence can help to give us an accurate representation of its impact[106]. Based on the findings from a systematic review and meta-analysis, the pooled prevalence of primary open angle glaucoma (POAG) is 3.05% (95% CI= 1.69-5.27), the pooled prevalence of primary angle-closure glaucoma (PACG) is 0.50% (95% CI= 0.11-1.36), and the pooled prevalence of all glaucoma is 3.54% (95% CI= 2.09-5.82)[106]. The pooled prevalence of glaucoma varies slightly depending on the world region[106]. It appears to be highest in Africa (4.79%), followed by Latin America and the Caribbean (4.51%), North America (3.55%), Asia (3.40%), Oceania (2.97%), and lowest in Europe (2.93%)[106]. The current number of people with glaucoma worldwide is 64.3 million and this number is expected to increase to 76.02 million in 2020 and to 111.8 million in 2040[106]. Based on this systematic review and meta-analysis, the projected number of glaucoma cases appear to be highest in Asia (66.83 million in 2040), followed by Africa (19.14 million in 2040), Latin America and the Caribbean (12.86 million in 2040), Europe (7.95 million in 2040), North America (4.72 million in 2040), and Oceania (0.42 million in 2040)[106]. Obviously the burden of glaucoma is high in the world and many people are undiagnosed until advanced disease leading to late treatment and worse outcomes[103, 107]. Due to the asymptomatic nature of glaucoma in its early stages, it is necessary to be aware of the risk factors associated with glaucoma to know one's risk of disease and need for screening[108].

2.2.2 Risk factors

Diabetes mellitus[109], hypertension[110], smoking[111], aging[112], thin average retinal nerve fiber layer (RNFL)[108], and high intraocular pressure[108, 113-116] are established risk factors for glaucoma[117]. With regards to treating glaucoma, high intraocular pressure (IOP) is the sole treatment target for

POAG[118]. Medication targeted to reducing IOP successfully reduced intraocular pressure in patients with glaucoma[114, 115]. There are vascular and mechanical theories explaining the effect of high intraocular pressure in detail, but essentially high intraocular pressure can damage the optic nerve[117]. The optic nerve is composed of nerve fibers and axons responsible for sending visual information to the brain[117]. Damage to this particular structure can lead to visual field defect, which is a key symptom of glaucoma[117]. One of the trademark symptoms of this disease is loss of retinal ganglion cells and/or axons, consequently leading to thinning of the RNFL[119]. Therefore, a thin average RNFL is commonly thought to be an early sign of glaucoma[119]. Finally, family history is also a risk factor[120]. The lifetime absolute risk of glaucoma for people with an affected family member is 22% compared to 2.4% for people without an affected family member[120]. Since a lot of cases go undiagnosed, it is also important to highlight some of the risk factors specific to undiagnosed glaucoma. Findings from a population-based study identified younger age, primary open-angle glaucoma (as opposed to angle-closure), no yearly glasses check, and no previous cataract surgery as risk factors associated with undiagnosed glaucoma[107].

2.2.3 Treatment

In the past years, there have been many advances in the treatment of glaucoma geared towards preserving the visual field of glaucoma patients and stopping optic nerve damage[121]. Glaucoma is primarily due to optic nerve damage. There is currently no medical or surgical treatment to reverse this process but lowering IOP does delay the progression of optic nerve damage[114, 115, 122]. The sole treatment target is reducing high intraocular pressure (IOP) and this can be done via medication, surgery, or laser therapy[122].

Although the ultimate role of drug agents in the treatment of glaucoma is lowering IOP, other factors such as tolerability, safety, enhancement of ocular blood flow, neuroprotection, and patient compliance should be taken into consideration[121]. Another important aspect to take into consideration is the mechanism of action of the drug[121]. Decreasing IOP can be achieved through decreasing aqueous production, increasing trabecular meshwork aqueous outflow (pressure-sensitive), or increasing uveoscleral aqueous outflow[121]. Topical beta-adrenergic antagonists are the standard medication of care for glaucoma and these antagonists lower IOP by reducing the production of aqueous humor[121]. However, there are many serious adverse events (depression, congestive heart failure, or chronic obstructive pulmonary disease) that should be taken into consideration when assessing how to treat glaucoma[121].

Surgical trabeculectomy consists of making a small hole in the eye to allow the aqueous humor to exit which ultimately will reduce the IOP[122]. Based on clinical trials, surgical therapy lowered IOP the most (by 60%), followed by medication (decrease of 49%) and laser therapy (decrease of 38%)[122]. However, the safety and efficacy are some of the most crucial aspects of any treatment and should always be transparently outlined to patients. A Cochrane systematic review and meta-analysis compared surgical trabeculectomy to non-penetrating surgery (NPS)[123]. Non-penetrating surgery is a term that encompasses glaucoma surgical techniques such as deep sclerectomy (DS), viscocanalostomy (VCO), and canaloplasty (CP) that have a similar goal to trabeculectomy[123]. Although each of the three non-penetrating surgery techniques are slightly different, they all share the common technique of no incision inside the eye[123]. These techniques mainly try to open and expose a structure named Schlemm's canal, which will increase aqueous flow through pathways and thus reduce intraocular pressure[123]. The findings of the Cochrane review and meta-analysis indicate that surgical trabeculectomy was more effective at reducing IOP in open-angle

glaucoma patients; however, the risk of complications was higher compared to non-penetrating surgery[123]. In fact, the absolute risk of dangerously low IOP (RR=2.3, 95% CI= 1.3-3.8), abnormal accumulation of fluid in suprachoroidal space (RR=3.9, 95% CI= 2.0-7.5), and cataracts (RR=3.4, 95% CI= 2.1-5.5) were all higher for the surgical trabeculectomy group[123].

Laser surgery is primarily focused on the trabecular meshwork, which is the part of the eye responsible for draining aqueous humor[122]. There are two types of lasers that are typically used to lower IOP; argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT)[122]. Compared to ALT, SLT tends to absorb less heat energy and therefore the risk of scarring or damage to the trabecular meshwork is reduced[122]. Although SLT and ALT are different, a systematic review and meta-analysis of six RCTs found that both SLT and ALT have similar effectiveness on lowering IOP[124]. Additionally, a Canadian-based RCT of 120 eyes followed over three, four, and five years found that the long-term effectiveness of lowering IOP between SLT and ALT was similar[125]. The effectiveness of lowering IOP is similar for laser and medical therapy[126, 127]. To sum up, there are two types of laser therapies used to treat glaucoma[122, 124]. Based on the evidence, the effectiveness between both types of lasers is comparable[124, 125], as well as the effectiveness between SLT and medication[126], and between ALT and medication[127].

In conclusion, glaucoma is characterized by optic nerve damage[102] initially impairing peripheral vision and has a global prevalence of 3.54%[106]. Diabetes mellitus[109], hypertension[110], smoking[111], aging[112], high intraocular blood pressure[117], thin RFNL[119], and family history[120] are established risk factors for glaucoma. The sole treatment target for glaucoma is lowering intra-ocular pressure and this can be done with medication, surgery, or laser therapy[122]. The risks and benefits of each should be evaluated before prescribing it to patients[121, 122]. Since the benefit of lowering

IOP is still unclear for individuals with borderline high pressure (21-24 mm Hg), these treatments might not be beneficial and might lead to adverse events[121, 122].

2.4 AMD and cognition/Alzheimer's disease

Cognitive decline can occur as a reality of normal aging, but can also occur as a result of neurodegenerative disorders[21]. The epidemiological evidence suggests that adults with cognitive deficits are more likely to develop dementia, which poses a significant burden on the population[11,21]. Alzheimer's disease (AD) is the most common form of dementia and is characterized by beta-amyloid, which are extracellular deposits[21]. There is some research assessing the relationship between AMD and AD, as well as AD and glaucoma, which will be underlined below.

A few investigators have compared the pathogenesis of Alzheimer's disease to the pathogenesis of AMD. Both diseases affect older adults, progress with time, and have similar risk factors such as aging, smoking and hypertension[128]. Furthermore, both AD and AMD share biological similarities, such as differences in the apolipoprotein E gene, and an excess of beta amyloid[128,129,130,131,132,133,134,135]. Both the retina and the brain are part of the central nervous system, which is likely why they share certain similarities[131]. For example, extracellular deposits can be found in the brain and in the context of AD are referred to as senile plaques[131]. Extracellular deposits (or drusen) are also found between the RPE and Bruch's membrane in AMD[131]. Small amounts of amyloid beta (Aβ) (amino peptides 36 and 43) are commonly found in the aging brain and in the aging retina[131]. Dentchev and associates found that Aβ deposits were found specifically in the drusen of the eyes affected with AMD and that none were found in

"normal eyes"[129, 131]. Additionally, there are many identical molecules found in the drusen (AMD) and in senile plaques (AD) such as proteoglycans, inflammatory mediators, metal ions, proteases, a2-macroglobulin, cholinesterases, serum amyloid P component, apolipoprotein E, and immunoglobulin[131]. Furthermore, the evidence suggests an association between apolipoprotein E type 4 allele (APOEe4) and AD[134], as well as with AMD suggesting a common pathogenic mechanism between the two disease[133]. Lastly, there is evidence that the functional polymorphism C in the gene encoding complement factor H (CFH) associated with AMD is also a risk factor for AD and that this particular polymorphism might interact with (APOEe4)[135]. The odds of AD were 24% higher among those with the CFH C polymorphism (OR=1.24, 95% CI= 1.02, 1.50)[135]. Further analyses demonstrated that this relationship was only seen in people who had the APOE e4 allele[135]. There are many pathological similarities between AD and AMD. However, what causes the two diseases is still unknown.

Some epidemiological studies have shown a relationship between AMD and cognitive impairment while others have not[11, 12, 14-16, 30]. Firstly, the Blue Mountains Eye Study, which is a population-based study of 3,509 individuals in Australia found a statistically significant association between AMD and cognitive impairment[30]. For the purposes of that study, cognitive impairment was defined by a Mini-Mental State Examination (MMSE) score between 0-23 or an MMSE-blind (omitting 5 items requiring good vision) score between 0-17[30]. After adjustment (age, sex, visual impairment, stroke, current smoking status, hypertension, alcohol consumption, and education), the odds of cognitive impairment (MMSE original scale) were 3.7 times higher (OR=3.7, 95% CI= 1.3-10.6) in adults with late AMD compared to adults with no AMD[30]. When looking at the association between AMD and MMSE-blind after adjustment, the odds of cognitive impairment were 2.2 (OR= 2.2, 95% CI= 1.0-5.0) times higher in adults with late

AMD compared to adults with no AMD[30]. Secondly, the Cardiovascular Health Study, which is a population-based prospective study of 2,088 individuals also found a statistically significant relationship between AMD and cognitive decline[136]. In this study cognition was measured using the Digit Symbol Substitution Test (DSST), which consists of translating 9 numbers with symbols underneath in 90 seconds[136]. Although the DSST is widely used to measure cognitive decline, it is a visual test, and might confound the association between AMD and cognitive decline. After controlling for co-variates (age, sex, ethnicity, study center, education, systolic blood pressure, total cholesterol level, diabetes, smoking status, and apolipoprotein E), it was found that the odds of early AMD were 2 times higher (OR=2.0, 95% CI= 1.29-3.10) for people with low scores on the DSST compared to people with higher scores[136]. Findings from two cross-sectional studies[11, 14] and a meta-analysis[12] support these results as well. A cross-sectional study conducted in Italy found that older adults with AMD performed worse on verbal fluency tests and memory tests compared to controls[11]. A hospital-based cross-sectional study conducted in Canada found that older adults with AMD had lower MMSE-blind cognitive scores compared to controls[14]. In addition, findings from a 2016 meta-analysis demonstrated that older adults with AMD had lower cognitive scores when assessed with the Mini-Cognitive test and the MMSE[12]. However, other studies have not found a statistically significant relationship between AMD and AD[15]. A recent case-control study measured the association and prevalence of AMD in patients with AD and found that after controlling for co-variates, the association was no longer significant[15]. To further examine this issue, a group of scientists in England conducted a cohort study to see whether people being admitted to the hospital with AMD were more likely to develop AD[16]. Hospital record linkage data from 1999 to 2011 were analyzed and the results showed no significant increased risk of AMD participants developing AD in future years (Rate

ratio= 0.86, 95% CI= 0.67,1.08)[16]. In sum, five studies reported a relationship while two studies have not and we still do not know why AMD and cognitive decline may be related.

2.5 Glaucoma and cognition/Alzheimer's disease

Researchers, clinicians and scientists are starting to group glaucoma in the overarching umbrella of neurodegenerative disorders[137]. This in part is due to neurodegenerative features associated with the disease such as neurodegenerative lesions in the optic nerve and visual cortex[137]. It also appears as though visual impairment is common in AD with research pointing towards glaucoma as being a cause of that visual impairment[137, 138]. Interestingly, glaucoma and AD do have pathological similarities, most notably the loss of neurons[137]. In glaucoma, this is presented as loss of grey matter in the hippocampus[139], retinal ganglion cells (RGC) and lateral geniculate nucleus (LGN)[140], while in AD this is presented as loss of hippocampal and cortical neurons[137].

In terms of the association between glaucoma and cognitive decline, there is mixed epidemiological evidence that mainly looks at prevalence of glaucoma in patients with Alzheimer's disease[103,141]. Only one cross-sectional study uses a neuropsychological test to measure cognitive decline[14]. A retrospective chart review study was conducted in a Canadian population and findings indicated that the prevalence of glaucoma was higher in patients with dementia due to Alzheimer's (DAT) compared to age-matched controls[17]. These results were replicated in a case-control study of 112 individuals from a German population, where 26% of older adults with Alzheimer's disease in a nursing home had glaucoma compared to 5% in the control group[142] and in a Japanese population, where 24% of adults with Alzheimer's disease also had glaucoma compared to a prevalence of 10% for controls matched for age and sex[143,18]. Nevertheless, in a register linkage study, glaucoma was not a risk factor for Alzheimer's disease

and findings from a 30 year follow-up study further support this conclusion[144, 145]. The Canadian cross-sectional study found that glaucoma patients displayed lower MMSE-blind cognitive scores compared to controls with normal vision[14]. Finally, Ou et al conducted a large retrospective cohort study that followed 63,235 participants for 14 years or until they were censored[19]. Patients included in this analysis were classified as having open-angle glaucoma (OAG) on at least two Medicare claims or who have received at least one diagnosis of OAG and one OAG related procedure[19]. The control group consisted of individuals who never had a Medicare claim for glaucoma or any glaucoma-related diagnosis[19]. Furthermore, anybody with a claim of a diagnosis of AD in the past three years were excluded at baseline[19]. The control group was matched to the OAG group using propensity scores[19]. The results of a Cox proportional hazards model demonstrated that individuals with OAG did not have an increased risk of developing AD compared to those without[19]. Therefore, this longitudinal analysis did not find evidence of a relationship between glaucoma and AD[19]. Lastly, a study in Denmark collected data on 11,721 patients with POAG at hospital discharge from the Danish National Hospital Register (DNHR)[145]. They did a Poisson regression analysis adjusting for sex, age, time from discharge, and substance use to estimate the risk ratio of dementia in individuals with POAG and found that POAG was not associated with increased risk of Alzheimer's disease[145]. However, the authors did highlight that because these data were taken from a register, there is a chance that no relationship was found due to misclassification[145]. In sum, the evidence is mixed; there is some concern that misclassification of glaucoma status could have biased some of the studies[145] and no investigation has been done into why glaucoma and cognitive decline might be related.

2.6 Eye disease, cognition, and brain imaging

Cognitive difficulties can be broadly defined as memory and attention difficulties, which are higher-order functions managed by the brain[21, 22]. Higher-order functions typically have a wide representation in the brain[146]. In other words, many areas of the brain such as the frontal and parietal networks are involved in the activation of such tasks (i.e., attention)[146]. There are various brain imaging measurements that can be used in cognitive research, with the goal of examining functional connectivity, and proteins that may be biomarkers for more serious cognitive disorders such as Alzheimer's disease[147].

Recently, there have been developments in brain imaging techniques that have broadened our understanding of the anatomical brain changes that occur in AMD and glaucoma[139, 148-150]. Although the brain can reorganize itself in the event of a disease to preserve cognitive functions, little is known about the specific brain processes that might drive the possible relationship between eye disease and cognition[150]. Based on brain imaging studies, adults with AMD had lower functional connectivity in the primary visual cortex and lateral occipital cortex[150], and volume reduction in the lateral geniculate bodies, and visual cortex[151] compared to controls[152]. Additionally, AMD was associated with a white matter decrease in the frontal lobe[151], which could be the connection between AMD and cognitive decline[152]. Volume reduction (decreased white and grey matter) in all structures along the visual pathway[152, 153], and grey matter volume decrease in the cerebellum, hippocampus, and fronto-orbital cortex[139] was seen in adults with glaucoma. Furthermore, decreased functional connectivity in the visual and working memory networks was also associated with glaucoma[139].

Understanding which structures of the brains of people with glaucoma or AMD are affected that could impact cognition could lead to specific preventative treatments[152], could potentially identify Alzheimer's disease biomarkers[147], and could potentially explain the epidemiological connection seen between eye disease and cognition.

Chapter 3: Cognitive activities

One reason eye disease and cognitive function may be related is via a reduction in cognitively stimulating activities due to vision loss (see Section 3.4). By cognitively stimulating, I mean activities that deeply stimulate cognitive skills such as problem-solving, motor control, analytical, memory, decision-making, language, etc. Highly cognitively stimulating activities would be activities like crossword puzzles, reading books, singing, playing cards, cooking, etc. Less cognitively stimulating activities would be activities that are more passive and do not challenge a person's cognitive skills (e.g. watching TV all day). There has been no research comparing the number of cognitively stimulating activities in those with and without eye disease. Some research, though, has been done examining difficulty in performing instrumental activities of daily living (IADL) (e.g. using telephone, shopping, laundry, medication management) in people with and without eye disease[154-156]. Difficulty with IADLs are an imperfect proxy for cognitive activities since many IADL activities are not very cognitively stimulating. Regardless, the consensus from current research assessing eye disease and IADLs is that older adults affected by eye disease (namely AMD and glaucoma) have more difficulties performing IADLs compared to older adults without these eye diseases[154,155,156].

3.1 IADLs and AMD

In 2014, a population-based cohort study assessed the relationship between AMD and IADLs, and the researchers found that adults with AMD had double the risk of IADL disability compared to older adults with no disability[154]. The authors speculated that IADL disability following AMD was most likely a result of reading difficulties[154]. Another study assessed the role of IADLs in the relationship between visual acuity and increased mortality[156]. They found that worse visual acuity was associated with a poorer score on the IADL questions[155-157]. Based on current epidemiological evidence, meal preparation, travelling, cleaning, grooming, shopping, going out, navigating steps and curbs, hobbies, watching television, reading, and driving are the activities most commonly affected by AMD[157]. Overall, there seems to be consistent agreement that AMD is associated with IADL difficulty[157].

3.2 IADLs and glaucoma

One study has been done to examine whether people with glaucoma report more difficulty with IADLs. In a pilot study with the goal of identifying everyday difficulties faced by adults with glaucoma, 63 participants were asked to rate the level of difficulty for a list of tasks[158]. Nearly half self-reported difficulties with walking on steps or curbs (49%)[158]. Other mentions included reading newspapers (43%), shopping (42%), crossing the road (36%), watching television (26%), indoor mobility (25%), visiting friends or restaurants (20%), housework and cooking (17%), and enjoyment of scenery (17%)[158]. Based on analyses of a visual disability questionnaire, outdoor mobility, glare and lighting, household tasks, and personal care were the most problematic for glaucoma patients[158]. Although this is a pilot study, it identifies difficulties engaging in certain

activities which supports the idea that glaucoma is associated with decreased frequency of participation in cognitive activities[158]. These difficulties are likely due to the amount of visual field loss in the eyes of glaucoma patients[159].

The studies mentioned above focus on only one eye disease and IADLs. The studies described below focus on both eye diseases and IADLs.

3.3 IADLs and eye disease

In 2012, Hochberg and colleagues evaluated whether adults with AMD or glaucoma encountered any disabilities with IADLs compared to controls[155]. The controls in this sample consisted of older adults who were suspected of having glaucoma or who presented with high intraocular pressure but had normal visual acuity and visual field test results[155]. The glaucoma group were diagnosed with primary open angle glaucoma with a visual field mean deviation worse or equal to -3dB[155]. Finally, the AMD group were diagnosed with bilateral AMD and visual acuity worse or equal to 20/32 in both eyes[155]. The findings from this secondary analysis showed that 45% of older adults with AMD and 25% of older adults suspected to have early glaucoma reported a disability in performing IADLs compared to 18% of the controls[155]. Furthermore, the likelihood of reporting a disability in performing IADLs increased when visual field loss for glaucoma and visual acuity loss for AMD were more severe[155]. In general, the current evidence demonstrates a relationship between eye disease and difficulties performing IADLs. Greater difficulty performing IADLs might eventually lead to the cessation of performing activities which are nonessential.

3.4 Cognitive activities and cognition

As highlighted in the prevention (1.2.3) and non-pharmacologic treatment (1.3.2) sections of cognitive impairment, living an active, cognitively stimulating life has been linked to less cognitive decline[51, 70, 82]. A longitudinal study of about four years in a sample of Catholic priests and nuns free of dementia at baseline identified the importance of engaging in cognitively stimulating cognitive activities for cognition[160]. In this study, participants were asked at baseline the amount of time spent watching television, listening to the radio, reading newspapers, reading magazines, reading books, playing games such as cards or chess, and going to museums[160]. Their analyses demonstrated that individuals who reported spending more time engaging in cognitively stimulating activities at baseline were less likely to develop Alzheimer's disease[160]. These findings align with the engagement hypothesis, which suggests that increased time spent engaging in cognitively stimulating cognitive activities leads to increased cognitive benefit[73, 160, 161]. Carlson and colleagues believed that participating in a wider variety of cognitive activities would engage different neurobiological pathways, similar to cross-training, and thus more effectively prevent cognitive decline[73]. They assembled a sample of community-dwelling older women and measured their participation in various cognitive activities through the Lifestyle Activity Questionnaire (LAQ)[73]. This questionnaire measures participation in 23 different cognitive activities (e.g. crossword puzzles, reading books, singing, attending church) based on a 6-point rating scale[73]. The researchers found that each additional activity per month reduced the risk of impairment in global cognitive outcomes by 8-11%, which supports their initial hypothesis[73]. They found that variety of cognitive activities, as opposed to adding up time regardless of the number of activities, was more strongly associated with change in cognitive

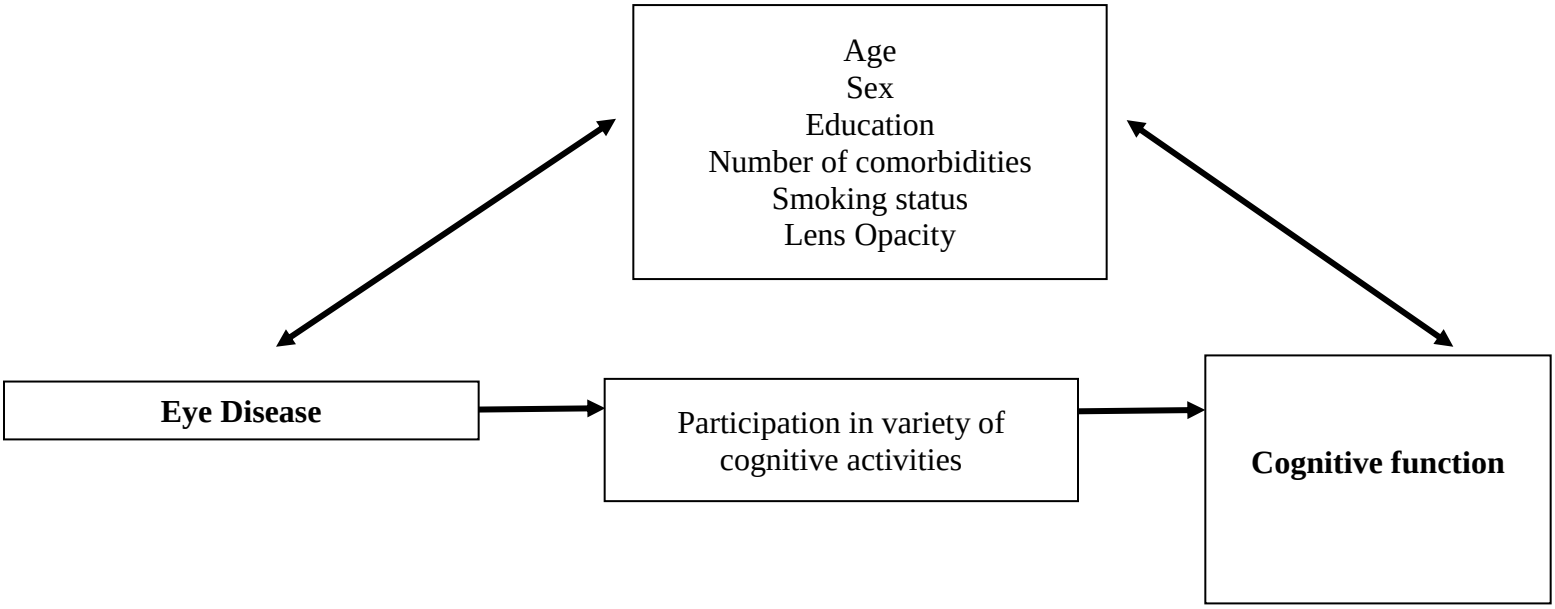
function in older adults[73]. No studies have examined the variety of cognitively stimulating activities and cognitive function in those with and without eye disease.

Cognitive Activities as a Mediator

We hypothesize that people with eye disease will have worse cognitive function that will be explained by a reduction in the variety of cognitively stimulating cognitive activities. One study has examined this but only in a very limited manner[162]. A three-year longitudinal study conducted in the United States, hypothesized that older adults with AMD who ceased six activities (reading, exercise/sports, hobbies, spectator activities, social activities, and cards/games) would experience greater cognitive decline compared to those who did not relinquish these activities[162]. Their findings supported their hypothesis and the multiple regression model from their analysis indicated that the number of activities was a strong predictor of cognitive decline[162]. For adults' younger than 80, each relinquished activity led to an increased risk of cognitive decline of 2.96 ($p<0.01$)[162]. This study, although intriguing, had several design weaknesses such as no control group with good vision, no glaucoma group, restricted number of activities, and a very limited cognitive assessment (one single questionnaire given only to informants)[162]. Our goal was to address this topic in more detail by studying large numbers of patients with late AMD or glaucoma and a control group with normal vision, using a battery of cognitive tests appropriate for people with vision loss, and using extensive data on cognitive, physical, and social cognitive activities.

Chapter 4: Conceptual framework

Figure 1: Conceptual framework for eye disease and cognition



This model depicts the conceptual framework (developed by Earp and Ennett)[163] of the hypothesized relationship between eye disease and cognitive decline. The box on the left on the model describes the eye disease exposure, which include AMD and glaucoma. The box on the right of the model includes the outcome (cognitive function). The box in the middle of the model is the hypothesized mediator (participation in variety of cognitive activities) between the exposure and the outcome. Lastly, the box at the top of the model includes the possible confounders that could impact the model. These variables will be used as co-variates in the analyses. Unidirectional arrows represent the direction of the hypothesized mediation, whereas bidirectional arrows represent potential confounding variables[163]. We propose that the cause of cognitive decline (e.g. aging, vascular condition, early stages of Alzheimers) does not matter in our conceptual framework because the participation in cognitive activities could delay the progression of all causes.

4.1 Rationale and Research Questions

Past research mentioned above describes a possible relationship between eye diseases and cognitive deficits. Yet, limited research has attempted to explain this relationship. To our knowledge, there is no epidemiological study with rigorous methods that has examined cognitive activities in groups with and without eye disease, or that examines whether cognitive activities mediate the relationship between eye disease and cognitive decline.

4.1.1 Research Questions and Hypotheses

1. Do older adults with glaucoma or AMD participate in fewer cognitive activities per month compared to older adults without one of these eye diseases?

   We hypothesized that older adults with glaucoma or AMD would participate in fewer cognitive activities per month compared to controls.

2. Are the reductions in activities in those with AMD or glaucoma due solely to specific subtypes of activities (e.g. physical, social, hobbies, novel information processing, etc).

   We hypothesized that patients with AMD would be affected across all activities but would have the lowest scores on activities using novel information processing due to their difficulties with reading.

   We hypothesized that glaucoma patients would generally be less affected than AMD patients except for physical activities due to difficulty with balance.

3. Do older adults with glaucoma or AMD experience worse cognitive function compared to older adults without one of these eye diseases?

   We hypothesized that older adults with glaucoma or AMD would experience worse cognitive function compared to controls.

We hypothesized that any relationship between glaucoma or AMD and cognitive function would be mediated by the number of cognitive activities they engage in.

Chapter 5: Methods

Most of the methods are described in the manuscripts. Here, I will just go into additional detail on certain methodological aspects.

5.1 Recruitment process

Participants were recruited from Hôpital Maisonneuve-Rosemont (HMR) (Montreal, Quebec) ophthalmology clinics from 2016-2017. The primary recruitment was done by a research assistant who recruited participants face-to-face when they came in for their appointments. The research assistant reviewed all of the charts of the people coming for their ophthalmology appointments the next day and based on their charts figured out who fit our inclusion criteria. These individuals were deemed as potentially phase 1 eligible. The following day, the research assistant approached the potentially eligible individuals in the waiting room. During this exchange, information about the study was provided and individuals were asked if they wished to participate. If they agreed, they were given a consent form, and data were collected that same day. In the odd case that data collection was not completed the same day, participants were asked to finish over the phone later. Each participant was compensated with $40.

5.2 Study design and population

The study design, sample description, and eligibility criteria can be found in both manuscripts. Although this study is a 2-year longitudinal study, I am only using the baseline data for my thesis

since the follow-up data are not collected yet. The sample is restricted to adults aged 65 and older since that is the age at which AMD and glaucoma tend to occur[164]. We wanted to exclude people with cognitive impairment from the baseline data collection. Therefore, any participant with a score that is less than 10 on the MMSE-Blind was excluded (indicator of cognitive impairment)[29, 165]. It is presumed that participants with a baseline MMSE-blind score higher than 10 are able to give reliable baseline data, are able to understand the nature of the research, and are able to consent to participating[165]. Participants with recent surgery (2 months or less) had to wait until at least 2 months had elapsed since it is likely that their level of participation in cognitive activities was reduced due to the surgery, which could bias the results. For our research questions, we were specifically interested in people with eye disease who had experienced at least some vision loss. The criteria for the AMD group (diagnosis of late stage AMD in both eyes and a better eye visual acuity worse than 20/40) was based on past literature using this cut-off to depict central vision loss[155, 166]. Finally, the criteria for the glaucoma group (diagnosis of POAG in both eyes and a visual field mean deviation worse than or equal to -4dB in the better eye) was based on past literature using this cut-off to depict mild visual field loss[167]. A flowchart illustrating the sampling process can be found in Appendix A.

5.3 Data Collection

5.3.1 Eye disease and vision data

Information on date of diagnosis, type of age-related macular degeneration (e.g. geographic atrophy), type of glaucoma (normal versus high tension), previous treatment for AMD, and number of current glaucoma medications was acquired from participants' medical charts. Data for visual acuity, contrast sensitivity in the worse eye, and visual field in the better eye were measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity chart

at 2 meters, the Pelli-Robson chart at 1 meter and the Humphrey FDT perimeter full-threshold testing, respectively. The ETDRS is a validated chart consisting of 14 rows with 5 letters in each row and is often used in clinical research[168]. In fact, it is the gold standard visual acuity measure in ophthalmology[169]. The Pelli-Robson chart is a validated and reliable chart that consists of pale grey letters on a white background to measure contrast sensitivity[170]. This chart makes it possible to detect eye disorders such as glaucoma early-on[170]. Finally, the Humphrey FDT is a valid and reliable[171,172,173] measure where patients are asked to press a button in response to different light stimuli across the visual field while fixating on a black dot[173]. This is widely used and allows ophthalmologists to detect visual field loss, especially for glaucoma[173]. These three tests were used for vision data collection because they each assess different areas of visual function that are associated with AMD and glaucoma.

5.3.2 Outcome: Cognition

Participants were verbally administered 7 cognitive tests: MMSE-blind version, one-minute verbal-fluency test letter and category versions, verbal digit span forward and backward tests, and the logical memory story using immediate and 20-minute delayed recall. The 7 tests took approximately 30 minutes in total to complete. These tests were chosen because they do not require good vision and touch on different cognitive skills.

MMSE-blind: The MMSE is used to screen cognitive impairment and is a questionnaire designed to assess a person's orientation, short-term memory, attention, language and recall. The MMSE-blind is a modified version of the 30-point questionnaire, which omits items requiring

good vision and has a maximum score of 22 points[29, 30]. It is widely used in clinical and research based settings and has been validated[29, 30].

One-minute verbal-fluency test: Participants were given a letter (e.g., p or s) and then a category (e.g., fruits or animal) and were asked to name as many words as they could in the given period (one minute)[174,175]. For example, they were asked to name as many words as they could that began with the letter P[174,175]. The verbal fluency test has been validated[176]. For individuals with dementia, the category fluency test has a sensitivity of 100% and a specificity of 92.5%, and the letter fluency test has a sensitivity of 89% and a specificity of 85% [176]. Although the one minute verbal fluency test assesses working memory, the category and letters components appear to rely on different cognitive processes[177]. The category fluency test seems to rely on access to word representations of semantic concepts[178] while the letter fluency test seems to rely on the central executive component of working memory[177, 179].

Verbal digit span forward and backward tests: This validated[180] test is used to assess working memory in which participants were given an increasingly long list of numbers and were asked to repeat the list in forward or reverse order[181,182]. This measure was used because it is presumed that the verbal digit span forward test relies on one of the main subcomponents of working memory (phonological loop), whereas the verbal digit span backward test relies on the other main subcomponent of working memory (central executive)[183]. The temporal, parietal and frontal lobes are the areas of the brain that are needed for the phonological loop component, whereas the prefrontal areas of both hemispheres are required for the central executive component[183].

Immediate and delayed logical memory: Participants were told a detailed short story involving an accident or an event and were asked to recall the story immediately and again 20 minutes later[184.185]. This test is both reliable and valid with a sensitivity of 92.2% and a specificity of 76.3% for cognitive impairment[186,185]. This test was used because it allows for examination of the encoding, storing, and retrieving processes of verbal memory[185]. Also, out of all the cognitive tests, it is the one that most closely resembles "every day memory"[185].

5.3.3 Mediator: Cognitive activities

Cognitive activities were assessed using the Victoria Longitudinal Study Activity (VLSA) questionnaire, which is a 70-item validated and reliable survey[187] assessing older adults' participation in various activities over the past 2 years[187]. A more detailed description of the scale can be found in the cognitive activities manuscript (Chapter 6). The VLSA scale was used to measure cognitive activities because we were specifically interested in examining the frequency of various activity participation (as opposed to length of time performing certain activities)[73, 187]. Also, this scale includes 70 different cognitive activities that many older adults in a focus group study reported valuing and performing[73, 187]. Subtypes of activities include physical, social, hobbies/home maintenance, novel information processing, and passive information processing. This scale was therefore chosen because it gives a wide range of activities that are representative of the older adult population[73, 187].

5.4 Analyses

5.4.1 Exploratory analysis

An exploratory analysis was done prior to running the primary analyses. Chi-square tests, t-tests, and Pearson's correlations were conducted to examine the association between the covariates and with the primary predictor and outcomes, as well as collinearity. Plots were generated to assess whether there were any potential outliers and to look at the distribution of the data for each variable. No outliers were present, but some of the continuous variables were not normally distributed. Collinearity was assessed among co-variates and none of the correlations were greater than 0.7 indicating little risk for collinearity.

5.4.2 Cognitive activities analysis

The Victoria Longitudinal Study Activity questionnaire consisted of 70 questions assessing frequency of participation in 70 different activities. The sum of each activity was calculated to create a variable representing the sum of activities done at least once per month, where the minimum score was 0 and the maximum score was 70. This variable was used as the cognitive activities outcome in a linear regression model to answer the first research question.

5.4.3 Cognition analysis

5.4.3.1 Quality control

To ensure that the six cognitive test outcomes were reliable and consistently scored, a quality control analysis was conducted. Since each cognitive test was administered verbally, participants were recorded, and a rater would later listen to each audio file and score the outcomes based on a given set of scoring guidelines. To assess the quality of the grading and whether scores differed depending on the rater, a second rater also listened to the audio files and scored each cognitive outcome based on the same set of scoring guidelines. Bland-Altman plots were generated to

evaluate the inter-rater agreement. Based on visual inspection of the Bland-Altman plots, the level of agreement among the two raters was quite high for all the cognitive outcomes except the immediate and delayed story theme scores. This is not surprising considering that the guidelines for scoring the themes were less rigorous and allowed for more subjectivity and variability in interpretation. Based on this finding, the immediate and delayed theme scores were not used in the main analyses. The six cognitive outcomes that were used in the main analysis were: verbal fluency letter, verbal fluency category, verbal digit span forward test, verbal digit span backward test, logical memory immediate story recall score, and logical memory delayed story recall score.

5.4.3.2 Main analysis

The verbal fluency letter score involved participants naming as many words as they could that started with the letter "P" in one minute. The total number of words mentioned in one minute was used and ranged between 1 and 27. The verbal fluency category score involved participants naming as many animals as they could in one minute. The total number of animals mentioned in one minute was used and ranged between 2 and 31. The verbal digit span forward and backward tests consisted of participants repeating a list of numbers in forward or reverse order. The total number of correct attempts was used as a cognitive outcome. The scores on the digit span forward test ranged between 3 and 16, while the scores on the digit span backward test ranged between 0 and 13. Lastly the logical memory story immediate and delayed recall consisted of participants recalling details of a story immediately and 20 minutes after it was told to them. The sum of items remembered was used as the outcome. Scores ranged between 0 and 21 for the immediate recall, while scores ranged between 0 and 19 for the delayed recall. The scoring sheet used for the logical memory test can be found in Appendix B. These six variables were used as

cognitive outcomes in six multiple linear regression models to answer the second research question.

5.4.4 Mediation analysis

The Baron and Kenny mediation analysis consisted of four main steps:

1- Demonstrate a statistically significant association between the eye disease (independent variable) and cognition (dependent variable); [188, 189]

2- Demonstrate a statistically significant association between eye disease (independent variable) and cognitive activities (hypothesized mediator);[188, 189]

3- Demonstrate a statistically significant association between cognitive activities and cognition when eye disease is in the model [188, 189];

4- Demonstrate that the coefficient for eye disease is less when activities is in the model[188, 189];

In addition to these steps, structural equation modeling (SEM) was performed to test the statistical significance of the mediator, otherwise known as the indirect effect. The mediation model framework can be found in Appendix C[190]. As shown in Appendix C, the total effect is the impact of eye disease on cognition[190]. The direct effect is the impact of eye disease on cognition that does not act through the indirect effect[190]. Full mediation would mean that the direct effect is zero and partial mediation would mean that the direct effect is reduced but is not equal to 0[190]. The indirect effect is the impact of eye disease on cognition that does act through the mediator[190]. SEM allows me to test the statistical significance of the indirect effect and to determine the proportion of the total effect that is explained by the indirect effect[190]. All mediation analyses were conducted using STATA Version 14 statistical software[191, 192].

5.4.5 Model fit

To ensure that the fit of the linear regression models was accurate, the assumptions of linearity, normality and homoscedasticity were checked for the cognition and cognitive activities models. This was done by visually assessing scatter plots, QQ-plots, normal quantile plots, and residual plots for curved or fan-shaped data. Bubble plots of cook's d, leverage and residuals were also generated to check for any presence of outliers or highly influential data points. Based on the plots generated, there were no violations of linearity for any of the cognitive outcomes. However, there were clear violations to normality for the subtypes of cognitive activities. Due to this, a linear regression with robust variance estimation technique (Huber/White/sandwich estimator)[193, 194] was used for the activity subtype models. The linear regression with robust variance consists of estimating the least square parameter estimates, which is done by reducing the residual sum of squares[193-195]. Standard errors can be estimated, which can control for the within sample variability of the linear regression parameter estimates[193-195]. This robust variance estimation analysis was done in Stata version 14 software and in SAS version 9.4 software[191, 192].

Chapter 6: (Manuscript 1)

Age-Related Eye Disease and Participation in Cognitive Activities

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MV contributed to the analysis, the interpretation of the data, and the drafting the manuscript. MJK, SB, GL, JR, and MHRG contributed to the interpretation of the results and the revision of the manuscript. SM collected the data, interpreted the data, and revised the manuscript. EEF contributed to the acquisition, analysis, and interpretation of the data and the revision of the manuscript. All authors gave final approval for the version to be published and agree to be accountable for all aspects of the work.

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Studies have found a benefit to living a cognitively active life in older age. Our goal was to quantify participation in cognitively stimulating activities in adults with and without age-related eye disease. We conducted a cross-sectional hospital-based study in Montréal, Canada of older adults (n=235) having either age-related macular degeneration (AMD) (n=65), glaucoma (n=64), or normal vision (n=106). To be eligible, the AMD group had to have bilateral late stage AMD with a better eye visual acuity of 20/40 or worse. The glaucoma group had to have a diagnosis of bilateral primary open-angle glaucoma with visual field mean deviation <= -4dB in their better eye. Further inclusion criteria included age ≥65 and a Mini-Mental State Exam Blind score ≥10. Cognitive activities were measured using the Victoria Longitudinal Study Activity Questionnaire. Linear regression was used. Patients with AMD (β=-4.8, 95% confidence interval (CI)= -6.8, -2.8) and glaucoma (β=-2.6, 95% CI= -4.3, -0.9) participated in fewer cognitive activities per month compared to those with normal vision after adjusting for age, sex, education, number of comorbidities, cognition, smoking status, and lens opacity. People with AMD and glaucoma participated in fewer cognitive activities, which could put them at risk for future cognitive impairment.

INTRODUCTION

Many observational studies have suggested the cognitive benefits of living an active, cognitively stimulating life[1-3]. For example, older adults who were more likely to engage in activities like reading, playing games, and going to museums were 33% less likely to develop Alzheimer's disease[1]. Researchers have found that the variety of activities that people participate in has been shown to be predictive of subsequent cognitive decline[3]. Research by Carlson *et al* found that each additional activity per month was associated with an 11% lower risk of incident cognitive impairment as measured using the Mini-Mental State Exam (MMSE)[3]. However, it may be difficult for people with age-related eye disease to participate in a wide variety of cognitive activities. Reduced cognitive activity participation may put older adults with eye disease at risk for cognitive decline and may explain why they seem to have lower cognitive scores[4-7]. To our knowledge, no prior studies have quantified the frequency of cognitive activities in people with and without eye disease.

Our primary objective was to determine whether people with age-related macular degeneration (AMD) or glaucoma, two of the most common causes of visual impairment in older adults, participate in fewer cognitive activities compared to older adults with normal vision. We chose an activity questionnaire developed by cognitive aging researchers that focuses on activities that are cognitively stimulating and that quantifies the time people spent doing various activities[8]. We hypothesized that patients with AMD and glaucoma would have reductions in total activities compared to people with normal vision. Our secondary objective was to determine whether any reductions in activities in those with AMD or glaucoma were due solely to specific subtypes of activities (e.g. physical, social, hobbies, novel information processing, etc). We hypothesized that patients with AMD would be affected across all activities but would have the lowest scores

on activities using novel information processing due to their difficulties with reading[9]. We hypothesized that glaucoma patients would generally be less affected than AMD patients except for physical activities due to difficulty with balance[10,11].

METHODS

Study Design and Population

Participants in this hospital-based cross-sectional study were recruited from the Hôpital Maisonneuve-Rosemont (HMR) (Montréal, Québec) ophthalmology clinics from 2016-2017. In total, we recruited 235 people in one of 3 groups that met the following inclusion criteria: 1) those with late stage AMD (geographic atrophy or neovascular disease) in both eyes with a better eye visual acuity of worse than 20/40, 2) those with a diagnosis of primary open-angle glaucoma in both eyes with visual field mean deviation worse than or equal to -4dB in their better eye, 3) and those who had normal visual acuity and visual field (better than 20/40 in both eyes and visual field mean deviation better than -4 dB in both eyes). The normal vision group did not have early or late AMD, glaucoma, or suspected glaucoma. The leading conditions for which the normal vision group were being seen included early stages of lens opacity, early stages of diabetic retinopathy, and posterior vitreous detachment. Exclusion criteria included if patients were under 65, if they had a score less than 10 on the Mini-Mental State Examination (MMSE) Blind Version, which is an indicator of cognitive impairment[12], or if they had eye surgery or other surgery in the last 2 months. Participants who had had surgery could participate after the 2 months had passed under the assumption that their activity levels and mood would be similar to pre-surgery levels[13]. Approval from the Ethics Committee at Maisonneuve-Rosemont Hospital was obtained. Written informed consent was acquired from each person. This research followed

the tenets of the Declaration of Helsinki. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Data Collection

Vision and Eye Disease

The Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity chart was used to measure binocular visual acuity at 2 meters wearing the normal prescription for distance correction[14,15]. Scores were converted to log of the minimum angle of resolution (logMAR). Visual field was measured using the Humphrey frequency doubling technology (FDT) perimeter full-threshold N-30 testing in each eye[16]. The medical chart was reviewed for details on the patient's eye disease (e.g. date of diagnosis, type of AMD) and any co-existing eye disease (lens opacity).

Cognitive Activities

All questionnaires were interviewer-administered in a face-to-face manner. Cognitive activities were measured with the Victoria Longitudinal Study Activity Questionnaire, which is a 70-item survey assessing older adults' participation in various cognitive activities over the past two years[8]. This test was found to have very good test-retest reliability[17]. Examples of activities included in the questionnaire are: gardening, exercise, preparing meals, doing housework, attending church, going shopping, giving a dinner party, engaging in sculpting/painting, working on crossword puzzles, writing letters or email, watching documentaries on television, etc. Each activity was assigned to one of 6 subtypes as determined by prior research (e.g. physical activities, self-maintenance activities, social activities, hobbies and home maintenance, novel information processing, and passive information processing)[8]. Respondents were asked to rate

the frequency of their participation for each item based on a 9-point scale (never, less than once a year, about once a year, 2 or 3 times a year, about once a month, 2 or 3 times a month, about once a week, 2 or 3 times a week, and daily). The total number of activities completed at least monthly was then used as the primary outcome[3], while the subtypes of activities done at least once per month were used as secondary outcomes.

Demographics and Health

Data were collected on each participant's age, sex, and number of years of formal education. The presence of current lens opacity was taken from each participant's medical chart. Participants were asked about a physician diagnosis of 13 chronic conditions (e.g. chronic obstructive pulmonary disorder, diabetes, arthritis). The MMSE Blind Version, which is an adaptation of the Mini Mental State Examination for adults with impaired vision, was administered[12]. Smoking status was obtained through self-report.

Statistical Analysis

To compare our three groups with and without eye disease, ANOVA and chi-square tests were used to assess whether there were any global differences in the number of activities done at least once per month. The normality of the total cognitive activity levels and each sub-group of activity levels was examined using standardized normal probability plots. To test whether total cognitive activity levels were different between the three groups, ANOVA was used. To test whether sub-groups of activity levels were different between the three groups, the Kruskal-Wallis test was used due to a lack of normality. For total activities, our primary outcome, linear regression was used to adjust for variables that were considered as potential confounders of the relationship between eye disease and activity levels like age, sex, education, comorbidity level,

cognitive status, smoking status, and lens opacity. For the subtypes of activities, linear regression with robust variance estimation (Huber/White/sandwich estimator) was used due to the non-normality of the distributions.

RESULTS

Of those patients that were thought to be eligible for age and diagnosis based on a review of the medical chart (n=751), 401 (53%) agreed to participate, 294 (39%) refused and 56 (7%) were not capable of answering by themselves. There were no statistically significant differences in age or sex between those who participated and those who did not (data not shown). Of the 401 who agreed to participate, 235 completed data collection, 128 did not meet the remaining eligibility criteria, and 38 did not complete data collection.

Demographic, vision, and health characteristics of the cohort can be found in Table 1. There were 235 Caucasian participants, of whom 65 had AMD, 64 had glaucoma, and 106 had normal vision. The groups with AMD and glaucoma were older, had less education, had worse visual acuity, worse visual field, and worse cognition. Furthermore, the AMD group contained more women and had more comorbidities.

Unadjusted results

As shown in Table 2, the AMD and glaucoma groups performed fewer physical activities ($p<0.001$), hobbies/home maintenance activities ($p<0.001$), passive information processing activities ($p=0.022$), and novel information processing activities ($p<0.001$) compared to the normal vision group. The largest difference was seen in the novel information processing group where the AMD group (median= 4.0, interquartile range (IQR)= 4.0) performed a median of 5

fewer activities per month than the normal vision group (median= 9.0, IQR= 4.0). The glaucoma group (median= 7.0, IQR= 4.0) participated in a median of 2 fewer novel information processing activities than the normal vision group (median=9.0, IQR= 4.0). In terms of the total number of activities performed at least once per month, both the AMD (mean= 17.0, SD= 5.8) and glaucoma (mean= 21.2, SD= 6.5) groups did fewer total activities per month compared to older adults with normal vision (mean= 25.7, SD= 5.2) ($p<0.001$).

Adjusted results

In Table 3, linear regression was used to adjust for demographic and health variables. Older adults in the AMD group performed 4.84 fewer total cognitive activities per month compared to older adults in the normal vision group (95% CI= -6.84, -2.83). The glaucoma group performed 2.60 fewer activities per month compared to the normal vision group after adjustment (95% CI= -4.34, -0.87). Other variables that were associated with total cognitive activities included age (β=-0.23, 95% CI= -0.34, -0.12) and education (β=0.31, 95% CI= 0.12, 0.50). As for the subtypes of activities, after adjustment, only AMD was associated with reduced physical activities (β=-0.57, 95% CI= -0.94, -0.20). Both AMD (β=-0.77, 95% CI= -1.20, -0.34) and glaucoma (β=-0.44, 95% CI= -0.82, -0.07) were associated with reduced hobbies and home maintenance activities. Finally, both AMD (β=-2.84, 95% CI= -3.90, -1.77) and glaucoma (β=-1.24, 95% CI= -2.17, -0.32) were associated with novel information processing activities. Neither AMD nor glaucoma were associated with social, self-maintenance, or passive information processing activities after adjustment (Appendix D).

DISCUSSION

Our study is the first to quantify the number of activities done by people with eye disease compared to people without eye disease. Patients with AMD did 4.84 fewer cognitively stimulating activities per month than older adults with normal vision. Most affected for AMD patients were physical activities, hobbies and home maintenance activities, and novel information processing activities, which includes activities like reading books, doing crossword puzzles, attending films or concerts, and doing volunteer work. This fit with our hypothesis that AMD patients would be affected across a variety of activities but that activities requiring novel information processing would be most affected. Patients with glaucoma were less affected although they still did 2.60 fewer activities per month than those with normal vision. Their scores were lowest for the subtype that included novel information processing activities, and this reached statistical significance.

The loss of visual acuity in AMD patients can lead to great difficulty with reading, driving, and exercising, which are abilities that are required for many of the activities that we examined[9,19,20]. Visual field loss due to glaucoma can also make it difficult to engage in activities as it has been associated with limited mobility, reading difficulties, driving modification and cessation, and crash[21-25]. Low vision rehabilitation can make these activities more feasible but many older adults do not participate[9,26,27]. Performing fewer cognitive activities could put patients with age-related eye diseases like AMD and glaucoma more at risk for cognitive impairment[1-3]. Indeed, research by Carlson *et al* found that each additional activity per month performed was associated with an 11% lower risk of incident MMSE impairment[3]. Many studies have documented reduced cognitive function in those with age-related eye disease but other studies have not[4-6,28-30].

Longitudinal studies are needed to determine whether adults with age-related eye disease have worse cognition because of performing fewer cognitive activities.

Our study is the first to quantify the frequency of activity levels as measured using a cognitive aging questionnaire in people with and without eye disease, and in particular, to look at variety of activities. However, other studies have examined difficulty with performing activities using questionnaires developed to assess visual disability. For example, Desrosiers *et al* measured visual disability using the Assessment of Life Habits questionnaire which measures 77 life habits, their degree of difficulty, and assistance used[31]. A 10-level score combined these two ratings. They found that 64 older adults with visual impairment recruited from a low vision rehabilitation clinic had lower scores than 64 people who had participated in an unrelated population-based study ($p<0.001$). Lamoureux *et al* measured a person's difficulty with doing activity levels using the Impact of Vision Impairment questionnaire, which comprises 32 items, in 319 people attending a low vision rehabilitation clinic and found that worse distance visual acuity was related to worse scores on several activity domains ($p<0.01$)[32]. These previous studies have concluded that people with eye disease have *more difficulty* performing various activities whereas our study conclusion is that people with eye disease are *less cognitively active*. Less cognitive activity may put people with eye disease at greater risk of subsequent cognitive decline[1,2].

The strengths of this study included the large numbers of people with AMD or glaucoma and having a comparison group with normal vision that was recruited from the same clinic. Our study was novel in using a questionnaire designed by cognitive aging researchers that focused on activities that are cognitively stimulating. A limitation is that our study is cross-sectional so we

cannot establish the temporality of the onset of vision loss and any reduction in the level of activities. Also, our refusal rate was 39% which is typical for a hospital-based study. We did not detect any statistically significant differences in age or sex between those who agreed to be in the study and those who refused so we think that the threat of selection bias is very low. Finally, these results may only be generalizable to AMD and glaucoma patients with bilateral disease who meet our acuity and visual field inclusion criteria.

Patients with AMD and glaucoma participated in fewer cognitive activities compared to older adults with normal vision, potentially putting them at risk for cognitive impairment. Efforts to increase their activity participation rate via low vision rehabilitation, occupational therapy, assistance from family and friends, and community programs should be explored[33].

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Table 1: Description of the study population

	AMD Mean (SD) or % n=65	Glaucoma Mean (SD) or % n=64	Normal Vision Mean (SD) or % n=106	p value*
Age, Years	83.9 (7.1)	77.8 (8.3)	72.8 (5.9)	<0.001
Sex				
Women	67.7%	62.5%	53.8%	0.175
Education, Years	9.5 (4.3)	11.1 (3.8)	12.4 (4.0)	<0.001
Binocular visual acuity, logMAR	0.74 (0.36)	0.23 (0.27)	0.04 (0.05)	<0.001
Visual field in better eye, MD in dB	-3.4 (5.2)	-9.4 (3.4)	1.4 (3.0)	<0.001
Mini-Mental State Exam Blind Score (max: 22)	19.5 (2.9)	20.0 (2.6)	20.9 (1.4)	<0.001
No. of comorbidities	3.2 (1.5)	2.9 (1.7)	2.6 (1.5)	0.057
Lens opacity	23.1%	15.6%	28.3%	0.167
Smoking				
Never smoker	34.9%	43.6%	43.8%	0.735
Former smoker	54.0%	50.0%	48.6%	
Current smoker	11.1%	6.5%	7.6%	

SD=standard deviation, MD=mean deviation, dB=decibels, logMAR=log minimum angle of resolution

*p value derived from ANOVA or chi-square test.

Table 2: Description of the sum of activities done at least once per month overall and by subtype of activity

	Physical Activities	**Self-Maintenance Activities**	**Social Activities**	**Hobbies and Home Maintenance**	**Passive Information Processing**	**Novel Information Processing**	**Total Activities**
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Mean (SD)**
Eye Disease Group							
Normal Vision	2.0 (1.0)	5.0 (1.0)	2.0 (1.0)	2.0 (1.0)	4.0 (1.0)	9.0 (4.0)	25.7 (5.2)
AMD	1.0 (2.0)	5.0 (1.0)	2.0 (1.0)	0.0 (1.0)	4.0 (2.0)	4.0 (4.0)	17.0 (5.8)
Glaucoma	1.0 (1.0)	4.0 (1.0)	2.0 (2.0)	1.0 (2.0)	4.0 (2.0)	7.0 (4.0)	21.2 (6.5)
Range	0-6	0-6	0-5	0-7	0-6	0-16	3-40
p value*	<0.001	0.393	0.234	<0.001	0.022	<0.001	<0.001

IQR=inter-quartile range, SD=standard deviation

*p value derived from Kruskal-Wallis test (activity subgroups) or from ANOVA (total activities).

Table 3: Linear regression models of relationships between age-related eye disease and total cognitive activities and subtypes of activities

Co-variates	Model 1 Total Cognitive Activities β	95% CI	Model 2 Physical Activities β	95% CI	Model 3 Hobbies and Home Maintenance β	95% CI	Model 4 Novel Information Processing β	95% CI
Eye disease group								
Normal vision	0.00		0.00		0.00		0.00	
AMD	-4.84	-6.84, -2.83**	-0.57	-0.94, -0.20**	-0.77	-1.20, -0.34**	-2.84	-3.90, -1.77**
Glaucoma	-2.60	-4.34, -0.87**	-0.24	-0.56, 0.08	-0.44	-0.82, -0.07*	-1.24	-2.17, -0.32**
Age	-0.23	-0.34, -0.12**	-0.01	-0.03, 0.01	-0.02	-0.04, 0.00	-0.08	-0.13, -0.02*
Female sex	0.65	-0.85, 2.14	-0.13	-0.40, 0.15	0.10	-0.23, 0.42	0.34	-0.45, 1.14
Education	0.31	0.12, 0.50**	-0.02	-0.05, 0.02	0.03	-0.01, 0.07	0.27	0.17, 0.37**
Number of Comorbidities	-0.11	-0.53, 0.31	-0.04	-0.12, 0.03	-0.06	-0.16, 0.03	-0.06	-0.29, 0.16
Smoking								
Never	0.00		0.00		0.00		0.00	
Former	1.04	-0.42, 2.50	-0.04	-0.31, 0.23	0.08	-0.24, 0.39	0.55	-0.22, 1.33
Current	0.05	-2.70, 2.81	-0.22	-0.73, 0.28	-0.15	-0.74, 0.45	0.39	-1.08, 1.85
Lens opacity	0.86	-0.79, 2.51	0.14	-0.16, 0.45	0.17	-0.19, 0.53	0.00	-0.88, 0.88
MMSE-Blind Score	0.31	-0.03, 0.65	0.08	0.01, 0.14*	0.00	-0.07, 0.08	0.14	-0.04, 0.32

*p<0.05, **p<0.01

Transition to Chapter 7

In the first manuscript we examined the association between eye disease and cognitive activities. The goal of this analysis was to examine the association between eye disease and the sum of cognitive activities done at least once per month. Through a multiple linear regression analysis of baseline cross-sectional data, we found that older adults with AMD and glaucoma participated in fewer activities per month compared to older adults without these eye diseases. This addressed the first research question of this thesis. The first manuscript has been accepted for publication in the Scientific Reports journal. The letter of acceptance can be found in Appendix E. The aim of the second research question was two-fold: 1) to examine whether there is an association between eye disease and cognition, and 2) whether this relationship was mediated by reduced participation in cognitive activities. One of our goals was to assess this relationship using more than one non-visual cognition measure (six were included in the analysis). The second manuscript examined the second research question. It will be submitted for publication once we have met the final sample size and have collected all of the data.

Chapter 7: (Manuscript 2):

Age-Related Eye Disease and Cognition

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MV contributed to the analysis, the interpretation of the data, and the drafting the manuscript. MJK, SB, GL, JR, and MHRG contributed to the interpretation of the results and the revision of the manuscript. SM collected the data, interpreted the data, and revised the manuscript. EEF contributed to the acquisition, analysis, and interpretation of the data and the revision of the manuscript. All authors gave final approval for the version to be published and agree to be accountable for all aspects of the work.

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Some studies have identified an association between vision loss and cognitive decline. Our objective was to assess whether older adults with age-related macular degeneration (AMD) or glaucoma would perform worse on six cognitive tests compared to older adults with normal vision. We conducted a hospital-based cross-sectional study in Montréal, Canada with 235 older adults divided into three groups: late stage AMD (n=65), primary open-angle glaucoma (n=64), and normal vision (n=106). Individuals in the late stage AMD had to have a better eye visual acuity worse than 20/40 and individuals in the glaucoma group had to have a visual field mean deviation worse than or equal to -4dB in their better eye. Participants were excluded from the study if they were under 65, or if they scored less than 10 on the Mini-Mental State Examination (MMSE) Blind version. Cognition was measured with six cognitive tests administered orally including the Verbal Fluency Test animal and letter versions, the Verbal Digit Span forward and backward versions, and the logical memory story with immediate and delayed recall. Linear regression models were used for all six outcomes. Compared to the normal vision group, the AMD group named fewer words per minute (β = -2.19, 95% CI= -4.08, -0.31) and the glaucoma group recalled less items immediately after the story was told (β = -1.73, 95% CI= -3.08, -0.38) and after a 20-minute delay (β=-1.51, 95% CI= -2.94, -0.09) after adjustment for demographic and health variables. These results were partially mediated by the number of monthly activities performed. Individuals with AMD and glaucoma showed some signs of poorer cognitive functioning, which could put them at risk for cognitive impairment.

INTRODUCTION

Many studies have found a relationship between eye diseases like age-related macular degeneration or glaucoma and cognitive decline[14, 18, 19, 30, 136, 142, 143]. However, very few have attempted to explain why eye disease and cognitive decline might be related. We hypothesized that the loss of vision late in life may lead to a dramatic reduction in cognitively stimulating activities, which research has shown increases a person's risk of cognitive decline[73, 160, 162]. One study has provided some evidence in support of this hypothesis. Rovner *et al* found that patients who had AMD and restricted their activities were more likely to experience cognitive decline 3 years later than AMD patients who did not relinquish activities[162]. This intriguing study needs to be followed up because it did not have a comparison group with good vision, it did not study glaucoma, and it assessed cognition using only the Mini-Mental State Exam Blind Version.

Our objectives were to examine whether older adults with AMD or glaucoma experienced worse cognitive function compared to older adults with normal vision and to determine whether activity level mediated any relationship between eye disease and cognitive function. Cognitive function was measured using six different cognitive tests that measure different aspects of cognition and that do not require good vision. We hypothesized that the AMD and glaucoma groups would perform worse on all six cognitive tests compared to the normal vision group.

METHODS

Study design and population

Participants in this hospital-based cross-sectional study were recruited from the Hôpital Maisonneuve-Rosemont (HMR) (Montréal, Québec) ophthalmology clinics from 2016-2017. In

total, 129 people in one of two eye disease groups that met the following inclusion criteria were recruited: 1) those with late stage AMD (geographic atrophy or neovascular disease) in both eyes with a better eye visual acuity of worse than 20/40 (n=65), and 2) those with a diagnosis of primary open-angle glaucoma in both eyes with visual field mean deviation worse than or equal to -4dB in their better eye, (n=64). The control group consisted of 106 adults with no diagnosis of AMD or glaucoma, and with a visual acuity better than 20/40 in both eyes and a visual field mean deviation better than -4dB in both eyes. Controls were most often being seen for an early stage lens opacity, posterior vitreous detachment, or early stages of diabetic retinopathy. Participants were excluded from the study if they were under 65, or if they scored less than 10 on the Mini-Mental State Examination (MMSE) Blind version. A score of less than 10 on the MMSE Blind could indicate some form of dementia, Alzheimer's disease or cognitive impairment and may lead to unreliable data[29, 196]. This study received approval from the Ethics Committee at Maisonneuve-Rosemont Hospital. Written informed consent was obtained from each participant.

Data Collection

Vision and Eye Disease

Information on date of diagnosis, type of age-related macular degeneration (e.g. geographic atrophy), type of glaucoma (normal versus high tension), previous treatment for AMD, and number of current glaucoma medications was acquired from participants' medical charts. Data for visual acuity and visual field in the better eye were measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity chart at 2 meters and the Humphrey Frequency Doubling Technology (FDT) perimeter full-threshold testing, respectively[171, 197, 198].

Visual acuity scores were converted to log of the minimum angle of resolution (logMAR), by convention.

Cognitive Outcomes

Participants were verbally administered several validated cognitive tests: one-minute verbal-fluency letter and category tests[176], verbal digit span forward and backward tests[180], and the 18-item story using immediate and 20-minute delayed recall[185, 186]. The tests took approximately 30 minutes in total to complete. These tests were chosen because they are validated cognitive tests that do not require good vision. All questionnaires were interviewer-administered in a face-to-face manner. For the one-minute verbal-fluency letter test, participants were asked to name as many words as they could in one minute that began with the letter P[174,175]. For the one-minute verbal-fluency category test, participants were asked to name as many animals as they could in one minute. The verbal digit span forward and backward tests were used to assess working memory. Participants were given an increasingly long list of numbers and were asked to repeat the list in forward or reverse order[181,182]. For the forward test, there were a maximum of 8 items with two trials each (16 trials in total) and for the backward test there were 7 items with two trials each (14 trials in total). One point per each correct trial was given. The test was stopped if a person missed both trials within an item. The last cognitive test administered was the logical memory story using immediate and 20-minute delayed recall. Participants were told a detailed short story and were asked to recall the story immediately and again 20 minutes later[184.185].

Mediating variable

Cognitive activities were measured with the Victoria Longitudinal Study Activity Questionnaire, which is a 70-item survey assessing older adults' frequency of participation in various cognitive activities over the past two years[6]. Participants used a 9-point scale (never, less than once a year, about once a year, 2 or 3 times a year, about once a month, 2 or 3 times a month, about once a week, 2 or 3 times a week, and daily) to rate their frequency of participation for each activity. The sum of activities done at least once per month was used as the mediating variable.

Demographics and Health

Demographic data such as age, gender, and level of education attained were collected. The self-report of a physician's diagnosis for 13 chronic health conditions (e.g., diabetes, heart disease, stroke, etc) was given by participants, and the total number of these health conditions was used as a measure of comorbidity. This measure of comorbidity has been used in previous studies of older adults with eye disease[199,165,200]. Smoking status was obtained through self-report. The presence of a current lens opacity (cataract) was taken from each participant's medical chart.

Statistical Analysis

Means, standard deviations, and proportions were calculated. Chi-square tests and ANOVA were used to assess the differences between the groups with and without eye disease. Normality was assessed with normal quantile plots. Multiple linear regression analysis was utilized to examine the relationship between eye disease and the cognitive outcomes. Linearity, normality, and heteroscedasticity were visually assessed through QQ plots and residual plots. There were no violations of the linear regression assumptions. Regression analyses were adjusted for co-variates

such as age, sex, education, number of comorbid health conditions, smoking, and lens opacity because of their potential importance to cognition according to prior literature[87, 91, 92, 165, 199-201]. The mediation analysis between eye disease, cognitive activities and cognition followed the Baron-Kenny mediation criteria. A formal test of the indirect effect was done using structural equation modeling with maximum likelihood with missing values estimation in Stata Version 14.

RESULTS

Demographic, health, and vision characteristics of the sample can be found in Table 1. All the participants were Caucasian, and a slight majority were women (54%). Adults in the AMD group were older, had worse binocular visual acuity, a lower number of years of formal education (mean=9.5, SD=4.3), and a higher mean number of health conditions (mean= 3.2, SD= 1.5) compared to adults in the glaucoma and normal vision groups. Older adults in the glaucoma group had worse visual field (mean= -9.4, SD= 3.4) compared to the AMD and normal vision groups. A larger proportion of adults in the normal vision group had mild lens opacities compared to the AMD and glaucoma groups (28.3% versus 23.1% and 15.6% respectively).

Unadjusted results

In unadjusted analyses (Table 2), people in the AMD and glaucoma groups performed worse on all of the cognitive outcomes compared to people in the normal vision group. The largest difference was seen in the verbal fluency letter and category scores, in which the AMD group mentioned approximately 4 words less per minute and the glaucoma group about 2 words less per minute compared to the normal vision group ($p<0.01$). The AMD group had mean verbal digit span forward (mean= 10.1, SD= 2.4) and backward (mean= 5.1, SD= 2.0) scores that were 1.3 and 1.4 points lower than the normal vision group ($p<0.01$). The glaucoma group had mean

verbal digit span forward (mean= 10.5, SD= 2.8) and backward (mean= 5.7, SD= 2.7) scores that were 0.9 and 0.8 points lower than the normal vision group ($p<0.01$). For the logical memory test, the AMD (mean= 8.1, SD= 5.0) and glaucoma (mean= 8.4, SD= 4.0) groups immediately recalled 2.8 and 2.5 items less than the normal vision group ($p<0.01$). After a delay of 20 minutes, the AMD (mean= 5.7, SD= 4.7) and glaucoma groups (mean= 6.1, SD= 3.9) recalled 2.9 and 2.5 items less than the normal vision group ($p<0.01$).

Adjusted results

A multiple linear regression adjusting for age, sex, education, comorbidities, smoking, and lens opacity was conducted to assess the relationship between eye disease and the cognitive outcomes (Tables 3a and 3b). Older adults with AMD mentioned 2.19 words starting with the letter "p" less per minute compared to those with normal vision (95% CI= -4.08, -0.31) but did not mention fewer animals. There was no statistically significant relationship between glaucoma and either verbal fluency outcome. Eye disease was not statistically significantly associated with verbal digit span forward or verbal digit span backward outcomes. Older adults with glaucoma immediately recalled 1.73 items less (95% CI= -3.08, -0.38) compared to the normal vision group and recalled 1.51 items less after the 20-minute delay (95% CI= -2.94, -0.09). There was no significant association between AMD and the immediate or delayed logical memory test.

Other variables besides eye disease were also related to the cognitive outcomes. Older adults performed worse on the verbal fluency category test, the verbal digit span forward test, and both the immediate and delayed memory test ($p<0.01$). Women performed better than men on the verbal fluency letter test and the verbal digit span forward test ($p<0.05$). Higher levels of

education were related to both verbal fluency tests, both verbal digit span tests, and the immediate recall of the logical memory test ($p<0.01$). Finally, former smoking was related to a better verbal fluency letter score, a better verbal digit span forward score, and current smoking was related to a better verbal digit span backward score ($p<0.05$).

Cognitive activities acted as a mediator according to the Baron and Kenny criteria (Table 4). After the addition of cognitive activities to each model, the beta coefficients for eye disease were no longer statistically significant. However, when formally testing the mediated (indirect) effect (Table 5), cognitive activities only statistically significantly mediated the relationship between AMD and verbal fluency explaining 62% of the total effect ($\beta= -1.31$, $p<0.01$) and glaucoma and the delayed logical memory test explaining 26% of the total effect ($\beta= -0.37$, $p=0.03$). Cognitive activities explained 18% of the relationship between glaucoma and the logical memory immediate test, although this indirect effect was only borderline statistically significant ($\beta= -0.28$, $p=0.05$). Figure 2 demonstrates the direct and indirect coefficients for the associations between AMD and verbal fluency letter, as well as glaucoma and logical memory.

DISCUSSION

In preliminary results, we found that patients with AMD and glaucoma had poorer performance on some cognitive outcomes. Individuals with AMD scored 2.19 words less on the verbal fluency letter test, whereas individuals with glaucoma scored 1.73 points less on the immediate recall of the logical memory test and 1.51 points less on the delayed recall of the logical memory test. We also found that cognitive activities acted as a partial mediator of these relationships.

These results partially support our hypothesis. Although we have not yet reached our final sample size, we expected to see lower cognitive scores on all tests for both eye disease groups. Instead our results support the conclusion that eye disease affects different aspects of cognition and that different eye diseases vary in their relationship with cognition. AMD and glaucoma impair vision in different ways; AMD mainly impairs central vision, while glaucoma initially affects peripheral vision and only late in the disease process affects central vision. This might explain why the association of each eye disease varied for each cognitive outcome assessed. AMD appears to be more strongly related to verbal fluency but only the letter version of the test. This finding is partially consistent with other studies[202, 203]. Clemons et el found that people with AMD having greater visual acuity loss had a lower mean verbal fluency letter score than those having less visual acuity loss. They also found a relationship with verbal fluency category scores[202]. Whitson et al found that 46% of older adults with AMD had a mean letter verbal fluency score that was one standard deviation (SD) below the mean for their age, gender, race, and education level, and that 18% of adults with AMD had a mean score that was two standard deviations below the demographic mean[203]. The effect of AMD on verbal fluency might be explained by brain-related changes[149]. Whitson et al also conducted a pilot study examining the role of brain connectivity in phonemic fluency in individuals with AMD[149]. In fact, there is brain-imaging evidence depicting a higher activation of the pre-frontal and parietal cortex during word processing tasks in adults with AMD[149, 204]. The authors hypothesized that because people with AMD have visual acuity loss, they utilize top-down attention during word processing tasks[149, 204]. Their findings provide support that AMD is associated with phonemic fluency deficits and that the AMD brain-related changes might cause these deficits[149].

Glaucoma appears to be more strongly related to the logical memory test than the other tests. There are limited epidemiological studies assessing the relationship between glaucoma and cognition. Furthermore, none of those studies examine immediate and delayed logical memory as cognitive outcomes[14, 17, 18, 141, 143, 205]. Nonetheless, there is some neurological evidence that is consistent with our findings[139, 148, 206, 207]. Firstly, there is a correlation of lower functional connectivity (FC) in both the visual and working memory networks with worse visual field[139]. Based on this, it can be theorized that in patients with severe impairment of visual field (such as individuals with glaucoma), decreased FC in visual and working memory networks could be due to maladaptation, thus contributing to clinical deficits such as difficulty remembering a story[139]. Secondly, the primary visual cortex has connections to other areas in the brain, such as the hippocampus, where visual input is integrated with other sensory information[148]. There is even evidence of loss of neurons in the hippocampus in people with advanced glaucoma[139]. Some studies have found a relationship between immediate recall of the logical memory story and left hippocampal volume[206]. This suggests a possible neurological link that supports our finding. Thirdly, another possible reason for the statistically significant finding between glaucoma and logical memory is the retinal nerve fiber layer thickness, which is related to visual field[207]. Based on past research, the RNFL appears to be thinner in people with primary open angle glaucoma compared to people with normal tension glaucoma[207]. A thinner retinal nerve fiber layer is also seen in patients with Alzheimer's disease, making it a possible biomarker for AD[208]. Furthermore, Shen et al demonstrated a correlation between RNFL and immediate logical memory[207]. Finally, an animal study found that chronically high intraocular pressure, as can be found in glaucoma, was associated with learning and memory impairments in rats[209].

We found evidence of partial mediation by cognitive activities, which are potentially modifiable through interventions such as low vision rehabilitation, cognitive training, and older adult activity groups. The ACTIVE trial found that cognitive training improved cognitive functioning in older adults but adults with vision loss were excluded from the trial[210]. Cognitive training programs targeted towards people with poor vision need to be developed and tested.

This is the first study to examine eye disease and cognition using two eye disease groups and several cognitive tests that measure different aspects of cognition that do not rely on good vision. Most studies looking at AMD and cognition, or glaucoma and cognition only use one cognitive test and only examine one eye disease[11, 12, 18, 30, 136, 143]. The fact that we included two eye disease groups with a control group from the same ophthalmology clinic is a strength. The multiple cognitive outcomes give a broader understanding of the different effect of AMD and glaucoma on cognition, which is also a strength. This study is not without limitations. Its cross-sectional design makes it impossible to establish the temporality between eye disease and cognitive decline. Because this is a single-site study and was restricted to participants with a certain degree of vision impairment, these results might not be generalizable to a population outside of Montréal, or to a population with visual acuity and visual field that do not meet our criteria. Lastly, cognition is a complex process and involves the interplay of various factors. Although we controlled our analyses with several demographic and health variables, it is possible that some important factors were not included which could create residual confounding.

Our findings add to the growing body of evidence that people with eye disease may be at risk for cognitive decline and add novel evidence that cognitive activities may partially mediate this

relationship. Longitudinal studies are needed to provide more rigorous evidence. Future work should further investigate the pathways that may explain the relationship between eye disease and cognitive function.

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Table 1: Descriptive characteristics of the study population

	AMD Mean (SD) or % n=65	Glaucoma Mean (SD) or % n=64	Normal Vision Mean (SD) or % n=106	p value*
Age, Years	83.9 (7.1)	77.8 (8.3)	72.8 (5.9)	<0.001
Sex				
Women	67.7%	62.5%	53.8%	0.175
Education, Years	9.5 (4.3)	11.1 (3.8)	12.4 (4.0)	<0.001
Binocular visual acuity, logMAR	0.74 (0.36)	0.23 (0.27)	0.04 (0.05)	<0.001
Visual field in better eye, MD in dB	-3.4 (5.2)	-9.4 (3.4)	1.4 (3.0)	<0.001
Mini-Mental State Exam Blind Score (max: 22)	19.5 (2.9)	20.0 (2.6)	20.9 (1.4)	<0.001
No. of comorbidities	3.2 (1.5)	2.9 (1.7)	2.6 (1.5)	0.057
Lens opacity	23.1%	15.6%	28.3%	0.167
Smoking				
Never smoker	34.9%	43.6%	43.8%	0.735
Former smoker	54.0%	50.0%	48.6%	
Current smoker	11.1%	6.5%	7.6%	

SD=standard deviation, MD=mean deviation, dB=decibels, logMAR=log minimum angle of resolution

*p value derived from ANOVA or chi-square test.

Table 2: Description of the primary and secondary cognitive outcomes

	Verbal Fluency Letter Mean (SD)	Verbal Fluency Category Mean (SD)	Verbal Digit Forward Mean (SD)	Verbal Digit Backward Mean (SD)	Immediate Story Recall Mean (SD)	Delayed Story Recall Mean (SD)
Eye Disease Group						
Normal Vision	14.2 (5.4)	16.5 (5.0)	11.4 (2.1)	6.5 (2.4)	10.9 (4.2)	8.6 (4.6)
AMD	9.9 (4.9)	12.6 (4.9)	10.1 (2.4)	5.1 (2.0)	8.1 (5.0)	5.7 (4.7)
Glaucoma	12.5 (4.9)	14.3 (6.0)	10.5 (2.8)	5.7 (2.7)	8.4 (4.0)	6.1 (3.9)
Range	0-27	0-31	0-16	0-14	0-25	0-25
p value*	<0.001	<0.001	0.002	0.001	<0.001	<0.001

SD=standard deviation

*p value derived from ANOVA test.

Table 3a: Multiple linear regression analysis of eye disease and verbal fluency letters, verbal fluency category and verbal digit span forward cognitive outcomes

Co-variates	Model 1 Verbal Fluency Letters β	95% CI	Model 2 Verbal fluency category β	95% CI	Model 3 Verbal digit span forward β	95% CI
Eye disease group						
Normal vision	0.00		0.00		0.00	
AMD	-2.19	-4.08, -0.31*	-0.46	-2.35, 1.43	-0.21	1.07, 0.66
Glaucoma	-0.98	-2.60, 0.64	-0.75	-2.37, 0.88	-0.64	-1.38, 0.11
Age	-0.09	-0.19, 0.01	-0.23	-0.33, -0.12**	-0.06	-0.11, -0.02**
Female sex	1.46	0.06, 2.87*	0.68	-0.73, 2.08	0.89	0.25, 1.53**
Education	0.40	0.22, 0.57**	0.27	0.10, 0.45**	0.15	0.07, 0.23**
Number of Comorbidities	-0.09	-0.50, 0.30	-0.06	-0.46, 0.34	-0.21	-0.40, -0.03*
Smoking						
Never	0.00		0.00		0.00	
Former	1.42	0.05, 2.79*	0.68	-0.70, 2.05	0.70	0.07, 1.33*
Current	0.09	-2.48, 2.67	1.84	-0.75, 4.42	0.82	-0.39, 2.02
Lens Opacity	-0.35	-1.90, 1.20	0.59	-0.97, 2.14	-0.52	-1.23, 0.19

*p< 0.05, **p<0.01

Table 3b: Multiple linear regression analysis of eye disease and verbal digit span backward, immediate and delayed recall of logical memory cognitive outcomes

Co-variates	Model 4 Verbal digit span backward β	95% CI	Model 5 Immediate logical memory β	95% CI	Model 6 Delayed logical memory β	95% CI
Eye disease group						
Normal vision	0.00		0.00		0.00	
AMD	-0.48	-1.32, 0.36	-0.36	-1.92, 1.20	-0.33	-1.96, 1.31
Glaucoma	-0.50	-1.22, 0.23	-1.73	-3.08, -0.38*	-1.51	-2.94, -0.09*
Age	-0.03	-0.07, 0.02	-0.17	-0.26, -0.09**	-0.21	-0.30, -0.12**
Female sex	0.61	-0.01, 1.24	0.96	-0.20, 2.13	0.70	-0.52, 1.92
Education	0.24	0.16, 0.32**	0.24	0.10, 0.38**	0.14	-0.01, 0.29
Number of Comorbidities	-0.08	-0.25, 0.10	0.27	-0.07, 0.60	0.29	-0.06, 0.64
Smoking						
Never	0.00		0.00		0.00	
Former	0.33	-0.28, 0.94	1.00	-0.14, 2.14	0.96	-0.24, 2.15
Current	1.60	0.43, 2.77*	0.25	-1.89, 2.40	0.32	-1.95, 2.58
Lens Opacity	-0.16	-0.84, 0.53	-1.16	-2.45, 0.13	-1.04	-2.38, 0.30

*p<0.05, **p<0.01

Table 4: Baron and Kenny mediation analysis of eye disease and verbal fluency, immediate and delayed logical memory cognitive outcomes using cognitive activities as the mediator

	Verbal fluency letter				Immediate logical memory				Delayed logical memory			
	Before mediator		*After mediator*		*Before mediator*		*After mediator*		*Before mediator*		*After mediator*	
	β	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
AMD	-2.19	-4.08, -0.31*	-1.15	-3.09, 0.79	-0.36	-1.92, 1.20	0.26	-1.37, 1.88	-0.33	-1.96, 1.31	0.32	-1.36, 1.99
Glaucoma	-0.98	-2.60, 0.64	-0.38	-2.00, 1.24	-1.73	-3.08, -0.38*	-1.35	-2.71, 0.02	-1.51	-2.94, -0.09*	-1.08	-2.50, 0.34
Cognitive activities			0.21	0.09, 0.34**			0.13	0.03, 0.24*			0.16	0.05, 0.27**

**Controlled for sex, age, education, number of comorbid health conditions, smoking, and lens opacity*

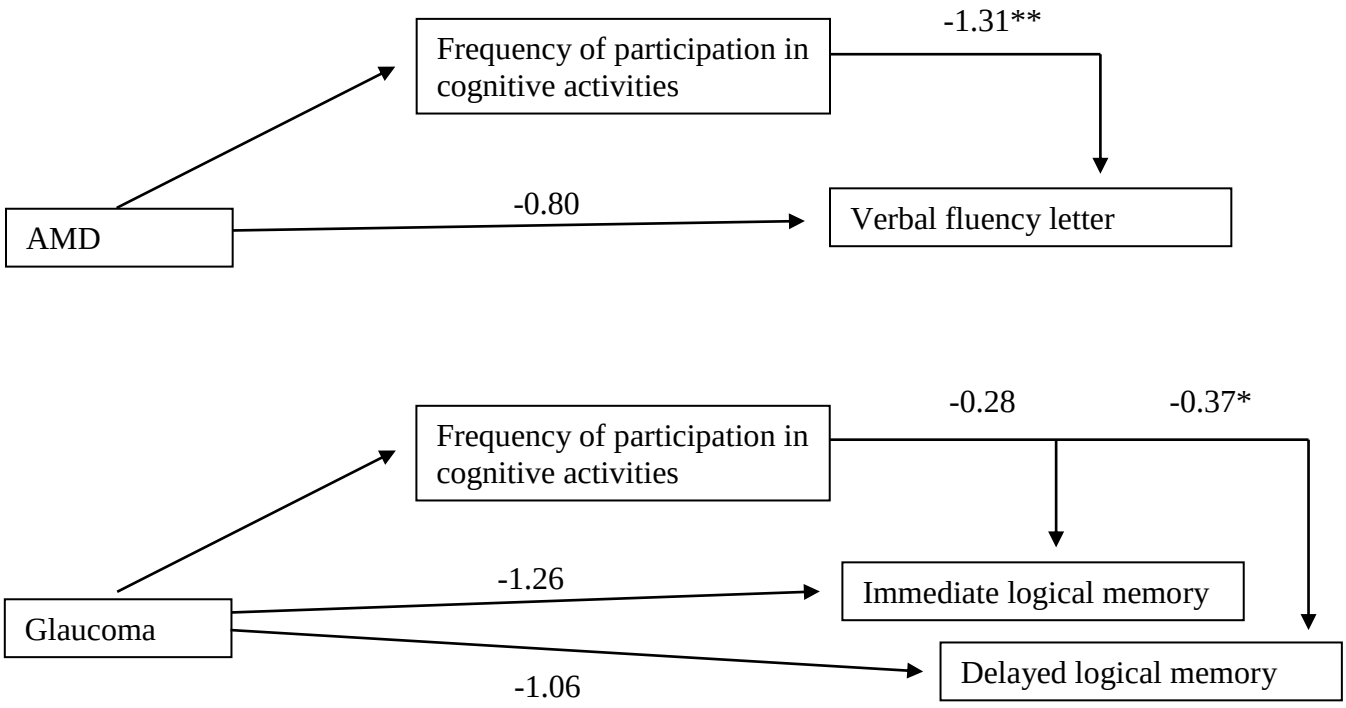
*p<0.05, **p<0.01

Table 5: Formal test of mediation using structural equation modeling

	AMD and Verbal fluency letter			Glaucoma and Immediate logical memory			Glaucoma and Delayed logical memory		
	β	**SE**	**p**	**β**	**SE**	**p**	**β**	**SE**	**p**
Total Effect	-2.10	0.99	0.03	-1.54	0.65	0.02	-1.42	0.63	0.02
Direct Effect	-0.80	1.08	0.46	-1.26	0.67	0.06	-1.06	0.64	0.10
Indirect Effect	-1.31	0.41	<0.01	-0.28	0.14	0.05	-0.37	0.16	0.03
Proportion Explained	0.62			0.18			0.26		

Controlled for sex, age, education, number of comorbid health conditions, smoking, and lens opacity

Figure 2: Mediation framework of direct and indirect effect of eye disease on verbal fluency letter and logical memory cognitive outcomes



*p<0.05
**p<0.01

Chapter 8: Discussion

Summary of findings and consistency with other research

In the current cross-sectional hospital-based study, AMD was statistically significantly associated with worse verbal fluency letter scores, and glaucoma was statistically significantly associated with worse logical memory scores (both immediate and delayed). These associations were partially mediated by the number of cognitive activities performed per month.

8.1 First research question: Cognitive activities

The findings from the eye disease and cognitive activities manuscript demonstrate the reduced participation in cognitively stimulating activities in older adults with AMD and glaucoma. These findings are novel, support our first hypothesis, and are consistent with the published literature[12, 154, 155, 157-159, 211-214].

For example, a prospective cohort study conducted in Germany found that severe vision impairment was associated with a decline in the weekly frequency of participation in seven cognitive activities[214]. In this particular study, they used a rather limited assessment of cognitive activities that included the frequency of reading, writing, doing crossword puzzles, playing music, attending social events, and playing card or board games, or social engagement[214]. Vision impairment was measured by asking participants to rate their vision on a three-point Likert scale (no impairment, mild or severe)[214]. Hochberg and associates examined whether AMD and glaucoma were significant predictors of instrumental activities of daily living (IADLs) disability[155]. They did find a significant association between AMD and IADL disability but failed to find one between glaucoma and IADL disability[155]. Their analyses indicate a gradient

effect between visual field, visual acuity loss and IADL limitation[155]. In fact, more severe visual field damage in glaucoma or visual acuity loss in AMD was associated with a greater likelihood of IADL difficulties[155]. The authors posited that a significant relationship was not found in their sample because visual field loss in the glaucoma group was mild or moderate[155]. When we limited our analysis to individuals with severe visual field loss, we found a stronger relationship between glaucoma and cognitive activities. This supports Hochberg et al's hypothesis that worse visual field leads to increased IADL disability[155]. An American cross-sectional study of visual field and activity disability also found a gradient relationship between visual field and activity limitation[215]. Their sample included 5,186 participants with normal visual field, as well as mild, moderate, and severe visual field[215]. Individuals with severe visual field deficits had greater odds of disability for driving limitations, IADLs, ADLs, and social activities compared to individuals with normal visual field or individuals with mild or moderate visual field deficits[215]. What is particularly noteworthy is that compared to those with normal visual field, the odds of limiting time spent participating in activities were 1.40 (95% CI= 0.96-2.03) and 1.66 (95% CI= 1.10-2.53) times higher for individuals with mild and moderate visual field defects[215]. However, the odds were much higher for individuals with severe visual field defects (OR= 5.06, 95% CI= 3.02-8.47)[215]. This indicates that although mild and moderate visual field loss can increase the odds of decreased activity participation, severe visual field loss has the largest impact[215]. Similar findings were also found in a 2016 study in which a higher number of individuals with severe glaucoma reported difficulties engaging in social roles (community/cultural/religious events, travel, social activities, familial relationships) compared to individuals with mild glaucoma[216]. There is evidence that glaucoma and AMD are associated with IADL difficulties[155] and decreased participation in cognitive activities, and that the strength of this association intensifies

with worse visual field[215, 216] or visual acuity[155]. Essentially, our work substantially adds to this body of knowledge by showing that people with glaucoma have lower activity levels across a wide range of activities.

Although there is evidence that both visual acuity and visual field are related to lifestyle activities, there appears to be variability between those two components of visual function in relation to the Melbourne Low Vision Activities of Daily Living Index (MLVAI)[217]. Haymes and associates examined the correlations between visual acuity, contrast sensitivity, visual field, and MLVAI[217]. Although they found significant correlations between all visual function measures and MLVAI, the strongest correlation was for the near visual acuity measurement (25cm), which is used for reading, while the weakest correlation was for visual field[217]. Perhaps the effect of visual acuity on IADL participation is more potent than the effect of visual field due to its importance for reading. This supports our finding that the association between glaucoma and cognitive activities was weaker in our data compared to the one between AMD and cognitive activities.

8.2 Second research question: Cognitive outcomes

Based on the unadjusted results, the eye disease groups had lower mean scores on all cognitive outcomes compared to the control group. The means for the verbal fluency and verbal digit span tests were higher in the control group compared to normative data, which can possibly be attributed to the higher mean age of the normative data sample[182]. The means of the logical memory scores were lower in the control group compared to normative data[218]. Considering that our control group was taken from an ophthalmology clinic and not from the general population, it is not surprising that the means of the cognitive outcomes are not completely identical to the

means of the normative sample. However, in general, the means of the cognitive outcomes of our control group are comparable to normative data[182, 218]. After adjustment, eye disease was only statistically significantly associated with three out of the six cognitive outcomes (verbal fluency, immediate logical story, delayed logical story). Since we expected a significant relationship between our eye disease groups and all cognitive outcomes after adjustment, these results only partially support our second hypothesis.

Other epidemiological studies have also found an association between eye disease (AMD and glaucoma) and cognition[11, 14, 30, 136, 142-144]. Most of this evidence either examined the prevalence of glaucoma[17, 142, 143] or AMD[15, 16] in older adults with Alzheimer's disease, or used a single cognitive measure like the Mini Mental State Examination (MMSE) scale to measure cognition[12, 14, 30]. Nonetheless, a study conducted by Rozzini and associates measured cognition using more than one scale to assess the association between AMD and cognition[11]. They took 51 patients with AMD and 24 matched controls and compared their performance on ten cognitive outcomes[11]. Similar to our findings, they did not find a significant association between AMD and all cognitive outcomes[11]. In fact, out of ten cognitive tests, only four were significantly different between AMD and controls[11]. Three of those measures included letter fluency, category fluency and immediate logical memory[11]. Consistent with our findings, there was a difference between the AMD and control groups for the letter fluency outcome, but not category fluency[11]. Unlike our results, this study found a statistical difference between the AMD and control groups for the logical memory test ($p=0.04$)[11].

There is limited published evidence examining glaucoma and cognition, and to my knowledge none that use the logical memory test to measure cognition[219-221]. There is one study that examined the relationship between glaucoma and multiple cognitive tests[219]. A study published in 2017 evaluated 41 individuals with POAG on various cognitive measures and compared their performance to 51 controls without a diagnosis of glaucoma and 21 older adults with Alzheimer's disease (AD)[219]. The mean scores of the glaucoma group were lower than the controls without a diagnosis of glaucoma for three memory tests (word list memory, delayed recall of the word list, and word list recognition test) and a verbal fluency test, but slightly higher than the AD group[219]. However, this study did not adjust for age, sex, or education so it's difficult to directly compare our findings. A population-based cross-sectional study of 1,179 individuals examined the association between age-related eye diseases (AMD, glaucoma, diabetic retinopathy, and cataract) and cognition[221]. In this study, cognition was measured with the Abbreviated Mental Test (ABT), which is a ten-question test of orientation, semantic knowledge, episodic memory, delayed recall, picture naming, and attention[221]. Cognitive dysfunction was defined as a score of six or less on the ABT and multiple logistic regression models were used to examine the association between each age-related eye disease and cognitive dysfunction[221]. After adjusting for age, sex, education level, income category, and type of housing there was no significant association between glaucoma and cognition dysfunction or AMD and cognitive dysfunction[221]. The authors did mention that only twelve cases of late AMD were included in their analysis, and that this lack of power might explain why the association between AMD and cognitive dysfunction was not significant[221]. They also stated that there is a lack of research looking at the association between glaucoma and cognition, and that the limited evidence available is conflicting possibly due to different study designs[221].

An important consideration to factor in when interpreting our results is whether glaucoma might impact short or long-term memory recall or both[219]. This is important because the mental processes that play a role in memory and encoding vary between short and long-term memory[219, 222]. Furthermore, one of the trademark symptoms of Alzheimer's disease is impairment in spontaneous recall or storage of new information[219], such as retaining information from the logical memory. The fact that we found a relationship between glaucoma and lower scores on the logical memory test after adjustment is evidence for cognitive memory impairment, which is a key symptom of AD. It is even common for short and long-term memory to interact when performing a cognitive test[222]. For example, the interaction between short-term and long-term memory, has been suggested to be highly important for the immediate recall of story memory[222]. In particular, individuals with preserved intelligence and intact executive functions are able to retain information in their short-term memory while identifying certain patterns in that new information and simultaneously accessing knowledge stored in their long-term memory to recode that information in a compressed representation that is less demanding on memory capacity (called chunking)[222]. This episodic buffer is critical to performance on the immediate logical memory story[223]. Perhaps the glaucoma group had lower scores on the immediate logical memory outcome because their ability to chunk information is compromised.

8.3 Third research question: Mediation

Based on the mediation analysis, we have provided cross-sectional evidence that cognitive activities mediated the relationship between AMD and verbal fluency letters, as well as the relationship between glaucoma and the immediate and delayed recall of the logical memory

score. To my knowledge, no research has assessed cognitive activities as a mediator between eye disease and cognition, which makes our results novel. Only one study has looked at the association between all three of these variables but in a limited fashion[162]. This study was a three-year longitudinal study and included 206 older adults all of whom had AMD[162]. A Poisson regression was used to model the incidence of cognitive decline in individuals with AMD who stopped engaging in 6 valued activities compared to those who did not[162]. The authors found that there was a higher risk of cognitive decline in adults with AMD in those who relinquished activities than in those who did not[162]. This supports our finding that activities mediated the relationship between AMD and verbal fluency. Longitudinal studies are needed to confirm this mediation since the temporality cannot be determined from cross-sectional data.

8.4 Limitations

Although these findings are interesting, there are a few limitations that need to be highlighted. Firstly, data collection for the 2-year follow-up was not available for this thesis project. Because only baseline data was available for these analyses, temporality between the onset of eye disease, cognitive activity limitations, and cognitive decline could not be established. For example, with cross-sectional data, you cannot rule out reverse causality (i.e. perhaps worse cognition resulted in doing fewer cognitive activities and resulted in the onset or worsening of age-related eye disease). Another caveat to highlight with a cross-sectional design are the results from the mediation analysis. Although there have been numerous cross-sectional mediation analyses performed, a mediation analysis assumes causality and that assumption can be trusted less with cross-sectional data. It would be preferable to conduct this same mediation analysis with longitudinal data. Secondly, it is possible that the study is subject to recall bias. For the Victoria Lifestyle Activities Questionnaire, older adults are asked to report how frequently they

participate in 70 different activities over the past 2 years. Although there are 9 different answers that can be given, it can be difficult to accurately recall one's engagement in 70 different activities over the span of 2 years. Participants might believe that they engaged in an activity more or less frequently than they did. Individuals with lower cognitive scores may have experienced greater difficulty remembering their frequency of participation than people with better cognitive scores. However, we do not think this difficulty with recall differed by eye disease groups so this would have resulted in non-differential misclassification and an underestimate of the true effect. Thirdly, the rate of recruitment was slower than we thought it would be, therefore we have not yet met our target sample size. Recruitment efforts are ongoing. Fourthly, this is a single-site study conducted in Montréal. The findings obtained might therefore not be generalizable to a population outside of Montréal. Fifthly, there might be selection bias in our exposure groups. For example, maybe individuals in the AMD and glaucoma groups were more tentative about participating if they had cognitive difficulties than people in the normal vision group. We tried to minimize the possibility of selection bias by having everyone approached in the exact same manner and by recruiting all eligible patients. There were no differences in age or sex between those who refused and those who accepted to participate. Lastly, cognition is multifactorial. Although we controlled for several potential confounding variables, there might still be residual confounding.

8.5 Strengths

This study also has quite a few notable strengths. Firstly, to our knowledge, it was the first study attempting to explain the relationship between eye disease and cognition by looking at mediation through cognitive activities. Secondly, it provided comparative data between AMD and

glaucoma, which is valuable considering the limited evidence in the literature. Thirdly, the use of several tests of multiple components of cognition allowed us to see which tests were more strongly related to AMD or glaucoma, which gives a greater understanding of their possible effect on the brain. Fourthly, since our control group was taken from the same ophthalmology clinic as the exposure groups, we think we minimized the risk of selection bias. Finally, we used cognitive tests that did not rely on vision.

8.6 Future Directions

8.6.1 Epidemiological steps

The findings from this thesis illustrate the potential implications between eye disease, cognitive activities and cognitive decline, which creates quite a few possibilities for future epidemiological research. Although longitudinal studies are required to establish temporality between eye disease and onset of cognitive impairment, there are other aspects of the methodological design that could help expand this field. Firstly, repeated-measures on the exposure, mediator and cognitive tests would not only help establish temporality, but could also allow us to look more closely at how a change in vision is related to changes in activities and cognition. That is, if eye disease and cognition are measured three to five times along a five to fifteen-year period, we would be able to examine whether changes in eye disease led to greater cognitive decline. Secondly, as was mentioned in the discussion of the second manuscript (Chapter 7), there is neurological evidence that could explain the association between AMD and verbal fluency letter, and the association between glaucoma and logical memory[139, 148, 149, 206, 207]. Future longitudinal repeated-measures studies should utilize brain-imaging technology to further delve into the workings of the brain pathways necessary for cognition. While participants would complete the cognitive

tests, their brain activity would be monitored using functional magnetic resonance imaging (fMRI) allowing observation of the functional connectivity between the different brain pathways involved in cognition[139, 149, 204, 206]. This would give answers on which areas of the brain are activated during each cognitive test for AMD and glaucoma, and whether there is actually a differential effect of AMD and glaucoma on cognition. This would also give insight on whether the effect of cognitive activities as a mediator changes over time. Finally, longitudinal studies with brain-imaging technology and repeated measures would establish temporality, and we'd be able to see whether reduction in cognitive activities occurs after eye disease and whether this mediates the relationship between eye disease and cognition.

8.6.2 Knowledge translation potential

If eye disease truly causes cognitive decline, there are several steps that could be taken to reduce cognitive decline due to vision loss. The development, testing, and implementation of a cognitive training tool that is auditory and not visual could be a worthwhile direction to take as this better caters to the large population of older adults with vision impairment. Another suggestion would be for low-vision rehabilitation programs to add cognitive training appropriate for those with vision loss as an option for their clientele. We are not aware of any low vision rehabilitation programs that currently do this although one pilot study adapted their low vision rehabilitation program to those who have mild cognitive problems. Twelve adults diagnosed with macular degeneration and who demonstrated mild cognitive deficits participated in a low-vision intervention program tailored to their cognitive abilities[224]. After the intervention, they had better scores on vision-related tests and cognitive tests[224]. Future work with larger sample sizes, a control group, and a cognitive training program designed to improve cognition and not just

functional vision is needed to determine whether this type of program could benefit adults with AMD and glaucoma. Since our findings demonstrate that greater variety in activity participation is associated with eye disease and cognition, retirement homes and nursing homes could ensure that their residents have access to a variety of cognitively stimulating activities. Governments could work harder to create communities in which older people can be active by investing in public transportation, well-lit sidewalks, and subsidizing activity programs for seniors.

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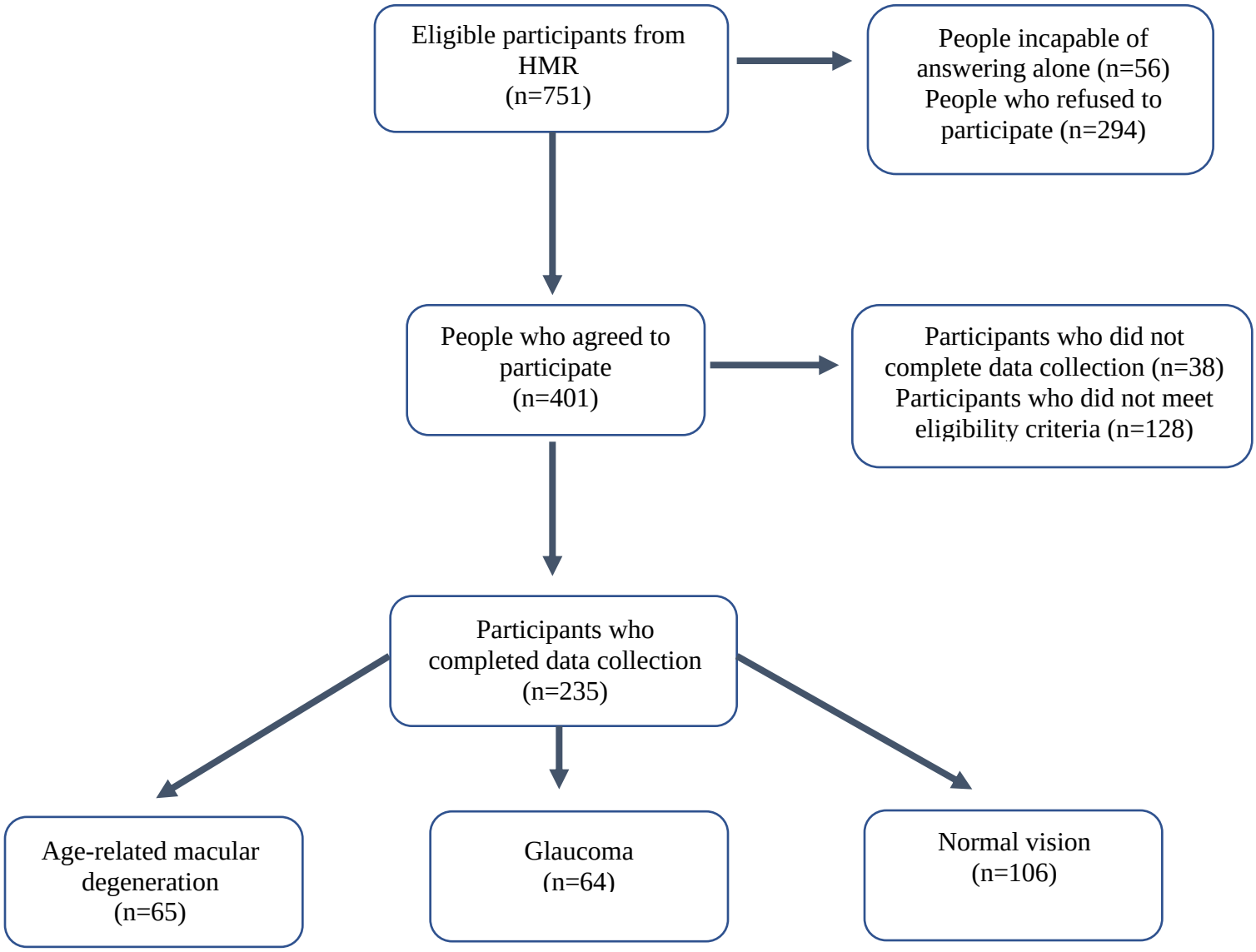
Appendix A – Sampling flowchart



Appendix B – Scoring sheet

1.1 LOGICAL MEMORY TEST I – IMMEDIATE RECALL

I am going to read to you a little story of just a few lines. Listen carefully and try to remember it just the way I say it, as close to the same words as you can remember. When I am through I want you to tell me everything I read to you. You should tell me all you can remember even if you are not sure. Are you ready?

> ***Anna Thompson of Montreal North, employed as a cook in a school cafeteria, went to the Police Station to report that she had been held up the night before on Sherbrooke Street and robbed of fifty-six dollars. She had 4 small children, the rent was due and they had not eaten for two days. The police, touched by the woman's story, took up a collection for her.***

Now what did I read to you? Tell me everything and begin at the beginning.
*(*You can prompt with *"Anything else?")*

Story1	Story	Theme	Scoring criteria
Anne			Or variation of name
Thompson			Thompson is required
Montreal			In any context
North			In any context
			Indication that the main character is a woman
Employed			Has a job/works
Cook			Or variation of name
Cafeteria			"Cafeteria" is required
School			"School" is required
			Indication that the main character works
Reported			Indication that a formal statement was made to someone in authority (in any context)
Station			Or word or phrase denoting a police station (headquarters, department)
Police			In any context
that she had been held up			An indication that she had been held up (i.e., gun point or knife)
Sherbrooke Street			In any context
night before			Indication that the hold-up occurred the previous night
robbed			Indication that a robbery took place
56$			>49$ and <60$
			Indication that the main character reported that she had been robbed
4			"Four" is required together with an indication that the children were hers
Small children			"Children" or a synonym is required (kids, little children, etc.)
			Indication that the main character has children
the rent was due,			Indication that the rent was due
they had not eaten			Indication that her children, or the family, were without food
for two days			"Two days" is required, or a phrase meaning about two days
			Indication that the main character was in need
police			A word or phrase signifying one or more members of the police department (in any context)
Touched by the woman's story			An indication that her story evoked sympathy
			Indication que la police éprouvait de la sympathie
took up a collection			A phrase indicating that money was collected
for her			An indication that the money collected was for her or her children

	[redacted]		*Indication that the police responded immediately to her need*

Recall (0 to 25)			Theme (0 to 7)

Immediate recall total score : _____/25; theme score : _____/7

Later on, I will ask you to tell me this story again, so try not to forget it.

LOGICAL MEMORY TEST I I- DELAYED RECALL

30 to 40 minutes after Logical Memoy I-Immediate recall

Do you remember the little story I read to you a few minutes ago? Now I want you to tell me the story again. Tell me everything; begin at the beginning

If no recollection: "*The story was about a woman who was robbed."*

*(*You can prompt with *"Anything else?")*

Appendix C – Mediation analysis framework

Figure 3a: Total effect of eye disease on cognition

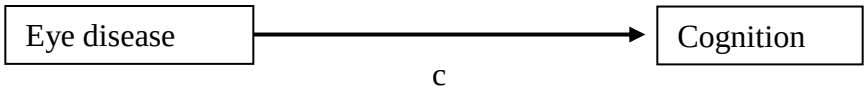
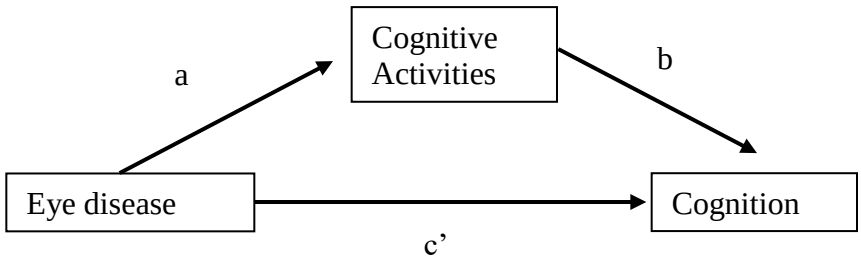


Figure 3b: Direct (c') and indirect (ab) effect of eye disease on cognition through cognitive activities



c = c' + ab

Appendix D – Relationship between eye disease and social, self-maintenance, or passive information processing sub-activities

Table 5: Linear regression models of relationships between age-related eye disease and social, self-maintenance and passive information processing activities

Co-variates	Model 5 Social Activities β	95% CI	Model 6 Self-Maintenance Activities β	95% CI	Model 3 Passive Information Processing Activities β	95% CI
Eye disease group						
Normal vision	0.00		0.00		0.00	
AMD	0.15	-0.32, 0.62	-0.21	-0.64, 0.21	-0.18	-0.68, 0.32
Glaucoma	-0.18	-0.59, 0.23	-0.26	-0.63, 0.11	-0.00	-0.44, 0.43
Age	-0.01	-0.04, 0.01	-0.02	-0.04, 0.01	-0.06	-0.08, -0.03*
Female sex	0.06	-0.29, 0.41	0.06	-0.25, 0.38	0.35	-0.03, 0.72
Education	0.00	-0.04, 0.05	-0.03	-0.07, 0.01	-0.01	-0.06, 0.04
Number of Comorbidities	0.10	-0.00, 0.20	-0.02	-0.11, 0.07	0.02	-0.08, 0.13
Smoking						
Never	0.00		0.00		0.00	
Former	0.06	-0.28, 0.40	0.27	-0.04, 0.58	0.03	-0.34, 0.39
Current	-0.77	-1.41, -0.12*	0.08	-0.51, 0.66	0.34	-0.35, 1.03
Lens opacity	0.12	-0.26, 0.51	-0.07	-0.42, 0.28	0.12	-0.29, 0.54
MMSE-Blind Score	0.00	-0.07, 0.09	0.07	0.00, 0.15*	0.03	-0.06, 0.11

*p<0.05

Appendix E – Letter of Acceptance Cognitive Activities Manuscript

Dear Prof Freeman,

We are delighted to accept your manuscript entitled "Age-Related Eye Disease and Participation in Cognitive Activities" for publication in Scientific Reports. Thank you for choosing to publish your work with us.

You should have just received another email from scirep.admin@nature.com with instructions for the next step, which is to complete your publication agreements. To continue with your publication agreements you will need to create a new account on this new system. Please complete these as soon as possible so we can start preparing your manuscript for publication. The agreements include the licence, which defines the terms of publication, and billing information for your Open Access article. Please see our FAQs page for further information about article processing charges.

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Best regards,

Dejian Lai
Editorial Board Member
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