Visual impairment, eye disease and their risk of depression and cognitive decline: The Canadian Longitudinal Study on Aging

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PREFACE

This thesis is original work by Alyssa Grant in contribution to the MSc Epidemiology research requirements. The research that makes up this thesis received ethics approval by the University of Ottawa in May 2019. Chapter Five of this thesis includes two manuscripts with co-authors Marie-Josée Aubin, Ralf Buhrmann, and Marie-Jeanne Kergoat entitled "Visual impairment, eye disease, and the 3-year incidence of depression: The Canadian Longitudinal Study on Aging" and "Visual impairment, eye disease, and the 3-year change in cognitive scores: The Canadian Longitudinal Study on Aging."

ABSTRACT

Objectives: Our goal was to explore the association between vision with cognitive change scores and incident depression.

Methods: A 3-year prospective cohort study was performed. Incident depression was defined using a cut-off score of 10 on the Center for Epidemiologic Studies Depression scale. Cognitive change was examined by calculating the difference between baseline and follow-up cognitive tests scores. Multivariable Poisson and linear regression were used.

Results: Cataract was associated with incident depression (relative risk=1.20, 95% confidence interval 1.05, 1.37). Visual impairment was associated with the 3-year change in Rey Auditory Verbal Learning Test (RAVLT) (β=-0.18, 95% CI= -0.28, -0.07), RAVLT-Delayed (β=-0.13, 95% CI= -0.25, -0.02), and Animal Naming Test (β=-0.95, 95% CI= -1.44, -0.45) scores. Glaucoma was associated with 3-year Mental Alternation Test change scores (β=-0.40, 95% CI -0.77, -0.04).

Conclusions: Cataract was associated with increased depression risk. VI and glaucoma are associated with 3-year changes in cognitive test scores.

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CHAPTER 1: INTRODUCTION

Aging is associated with an increase in vulnerability to pathology and functional limitations resulting from declines in both physical and cognitive health[1]. The growth of the older adult population has led to ever-larger numbers of individuals reaching ages where functional limitations are more common. Age-related eye disease is one example of a pathology that is more common in older age. The loss of vision, particularly late in life, can have large societal consequences. Older adults with visual impairment (VI) may have difficulty with many tasks that allow them to remain independent and to enjoy a good quality of life.

VI has become increasingly common in community-dwelling Canadian adults; the prevalence in those aged 45-85 years is 5.7% and increases progressively with increasing age with a prevalence of 15.6% found in those aged 75-85 years [2]. VI is most often defined by visual acuity which measures the power of the visual system to discriminate on a spatial basis[3] and is typically measured using a letter chart such as the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart following a standard protocol.[4] Either presenting visual acuity, in which people wear their normal correction for distance, or best-corrected visual acuity, in which all refractive error is removed, can be measured. For research purposes, the United States criteria for the definition of VI is typically used in which presenting visual acuity worse than 20/40 is indicative VI.[5] An individual with 20/40 vision sees at 20 feet what someone with normal vision sees at 40 feet.

Data from a recent population-based cross-sectional study reported that uncorrected refractive error was the leading cause of VI in Canada.[2] Age-related eye diseases including cataract, age-related macular degeneration (AMD), and glaucoma have also been identified as

major causes of VI and blindness[6] and were reported in 2-7% of the Canadian population.[2] Less common causes of VI include visual pathway and other retinal diseases, corneal disease, and diabetic retinopathy[6]. Several risk factors have been identified to be related to VI and include: lower income, current smoking, memory problems[2]; older age[2,6]; diabetes[2,7]; female sex[8]; and living in a rural area[9].

There are many health implications and activity limitations associated with VI that have been studied among older adults that extend well beyond the visual system and include: decreases in quality of life[10], less participation in leisure activities[11], worse performance of activities of daily living (ADLs) and instrumental activities of daily living (IADLs)[12], worse cognitive function[13], and increases in depressive and anxiety disorders[14,15], falls[16,17], hip fractures[18–20], and social isolation[21]. VI has been found to amplify the effects of other comorbid conditions and also can reduce an individual's ability to effectively manage a chronic disease by reducing the ability to self-care, transport to appointments, and administer medication thereby increasing costs to the healthcare system and worsening health outcomes[22].

Much of the research on the health implications of VI has been cross-sectional. Cross-sectional research is limited because the temporality of the exposure and the outcome cannot be established. My thesis focused on utilizing longitudinal data to understand if people with VI and age-related eye disease have a higher risk of depression or cognitive decline, two conditions that can have a devastating impact on a person's ability to live independently. Chapter 2 of my thesis will review the literature on this topic. Chapter 3 will present my study aims. Chapter 4 will describe the Canadian Longitudinal Study on Aging, which will be the data

source for my thesis. Chapter 5 will include a manuscript for publication. Chapter 6 will include supplemental results and Chapter 7 will integrate the results together for discussion.

CHAPTER 2: LITERATURE REVIEW

This thesis will focus on whether depression or cognitive decline are more common in those with VI or age-related eye disease. The literature on depression will be reviewed first followed by the literature on cognitive function.

Major depressive disorder

Clinical major depressive disorder (MDD) is a commonly occurring mood disorder, with an estimated lifetime prevalence of 11.2% reported in the general Canadian population. [23] MDD is a multifactorial disorder involving a complex interplay of predisposing personal, genetic, biological, societal and environment factors, generally following a chronic course with considerable morbidity, has a high rate of relapse and recurrence and is associated with significant impairment in both social and occupational functioning[24–27]. According to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V),* five of the following symptoms must be present continuously for a 2-week period for an appropriate diagnosis of MDD and at least one of the symptoms should be either (i) depressed mood or (ii) loss of interest or pleasure: (i) depressed mood; (ii) loss of interest or pleasure; (iii) significant weight or appetite alteration; (iv) psychomotor agitation or retardation; (v) fatigue or loss of energy; (vi) feelings of worthlessness or excessive or inappropriate guilt; (vii) diminished ability to think or concentrate or indecisiveness; and (viii) suicidal ideation[28]. Severity of MDD is classified based on the number of criterion symptoms, the severity of those symptoms and the degree of functional impairment[28]. In order to operationalize depression without reliance on a clinical expert, researchers have developed symptom checklists and rating scales such as the

Center for Epidemiologic Studies- Depression (CES-D-10) Scale, a self-report measure of depressive symptomatology[29]. The CES-D-10 consists of 10 items such as "I was bothered by things that usually don't both me: 0 = rarely or none of the time; 1= some or a little of the time; 2= occasionally or a moderate amount of time; 3= all of the time." A total score is calculated by finding the sum of 10 items; a score of 10 or greater is indicative that an individual has major depressive symptoms. The CES-D-10 has been confirmed to be a reliable and valid measure of depression in community-dwelling older adults[30].

Current treatment practices

Management of MDD depends on the disease severity and typically consists of a combination of psychotherapy and pharmacological treatment, modulated according to the patients' illness course[31,32].

Pharmacological treatment:

The main classes of antidepressant medications currently used in the treatment of MDD include monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin-reuptake inhibitors and serotonin/noradrenaline-reuptake inhibitors[33]. The efficacy of antidepressant medication is very well-established with some indication that efficacy is comparable within and between classes; approximately one-half of patients will respond to any prescribed antidepressant medication irrespective of its class, and a large portion of the other half will be responsive either to another antidepressant medication or to a combination of antidepressant medicationss[33]. However, antidepressant medication appears only to suppress the depressive symptoms and there is a lack of evidence that the risk of recurrence is reduced once antidepressant medication use is terminated[34].

Psychotherapy:

Several forms of targeted psychotherapy that have been combined or sequenced with antidepressant pharmacotherapy exist and include cognitive therapy[35], interpersonal psychotherapy[36], the cognitive-behavioral analysis system of psychotherapy[37,38], problem solving therapy[39], and psychodynamic-interpersonal psychotherapy[40]. In patients with MDD, pharmacotherapy and psychotherapy treatment have been found to be about equally effective, with the exception of selective serotonin-reuptake inhibitors which have shown slightly more efficacy than psychological interventions[41]. Studies comparing the two treatment types, however, have found smaller dropout rates in psychotherapy interventions compared with pharmacotherapy[41].

Recent research has found that the effects of combined treatment consisting of pharmacotherapy and psychotherapy are additive, may be largely independent of one another, are not associated with baseline disease severity and remained significant upon completion of treatment[42]. Despite the availability of several efficacious treatments and strategies, MDD frequently goes unrecognized and, when recognized, various factors including age, gender and the presence of comorbid conditions are related to the uptake of treatment [43]. For example, it has been reported that age is inversely associated with receiving treatment for depression and as a result under-treatment is more common among older persons[44]. Previous studies have also found that men use antidepressant medications to a lesser extent than women[45,46]. Potential explanations for this sex difference include the fact that women are more prone to the somatic symptoms of depression and are more likely to seek healthcare than men, who tend to present more melancholic symptoms[47,48]. Further, among older adults, physical frailty, medical

comorbidities, and cognitive impairment were found to be associated with an increased likelihood of receiving treatment which may be due to the increase in somatic symptoms of depression present among these individuals.[44] In fact, recent Canadian data suggest that 28% of individuals with probable MDD report not receiving any help for their condition[49]. Further, even when MDD is diagnosed and treatment is prescribed, many patients still fail to follow the treatment properly[43]. Several barriers of adherence to MDD treatment have been identified and include patient-specific (erroneous beliefs, forgetfulness, negative attitudes, comorbidity and lack of knowledge), medication-specific (side effects, costs, treatment duration), social-cultural (lack of support system, religious and/or cultural beliefs, stigma) and logistic (poor access to healthcare) barriers as well as issues regarding healthcare provision (multiple prescribers, long wait times, poor communication with healthcare providers, frequent medical visits and/or medication refills)[50].

Risk factors for MDD

Risk factors associated with depression across the adult lifespan include biological factors and medical conditions (endocrine, inflammatory, cardiovascular and neuroanatomical factors[51]), psychological and social factors (such as personality traits including high neuroticism, low conscientiousness, low extraversion, low agreeableness, low openness and low mastery, loneliness, not having a partner, recent negative life events and having a smaller social network[51]), health behaviours (alcohol consumption, low physical activity, smoking[51], and sleep disturbance[52]), genetic factors (heritability in first-degree offspring of MDD patients[53]) and demographic factors (female sex and low education[51]). The female: male ratio of global disability from MDD is 1.7:1, which may be related to both socioeconomic and biological

factors[54]. Further, there is evidence of a bidirectional relationship between biological and psychosocial risk factors with MDD in that the demands of managing chronic medical conditions, functional limitations and pain can lead to the onset of more depressive symptoms and therefore in turn, MDD makes it more difficult to treat the condition or disease[51].

Specifically among older adults, risk factors contributing to the onset and maintenance of MDD likely comprise of complex interactions between age-related vulnerabilities including genetic factors, cognitive diathesis, neurobiological changes and the types of stressful events that occur with greater frequency in late life[55]. Many of the changes associated with aging, such as functional and cognitive limitations, pervasive negative stereotypes and role changes could lead to negative self-evaluation and to a reduction in participation in activities and thus reduced engagement with the environment which increases the risk of depressive symptomatology in older adults, especially among those with existing vulnerabilities[55].

Visual Impairment, eye disease & depression

As we mentioned above, medical conditions can be associated with depression. This thesis is focusing on the relationship between VI and age-related eye disease with depression. A summary of the literature on this topic will be presented.

Cross-sectional study findings:

Findings from cross-sectional studies have shown that there is an increased prevalence of depressive disorders among those with commonly occurring age-related eye diseases such as AMD[56], glaucoma[57], cataract[58] and among those with VI[15,56,59–64], as compared to those with normal vision. It has been suggested that the functional impairment that is commonly experienced among those with vision loss may contribute significantly to the onset of such

depressive symptoms[59,63,65]. Studies examining patients of outpatient eye clinics and low-vision rehabilitation services have identified several risk factors for depression among these patient populations including: non-white ethnicity[64]; total number of eye conditions[64]; younger age[61,64]; female sex, living alone, having lower acceptance of vision loss[61]; having a history of mental health problems[61,62]; having an avoidant coping style, lower perceived adequacy of social support, higher levels of vision specific distress[62]; poor self-reported visual functioning[62,64]; poor self-reported health[61,62,64]; and higher level of comorbidity[56,60]. However, since the associations between eye disease and VI with depression were examined using cross-sectional data in these studies, it does not allow for delineation of the temporality or the identification of pathways leading to increased risks[15,56,58–64].

Longitudinal Study Findings:

Only a limited number of longitudinal studies have assessed the association between age-related eye diseases and VI with depression[10,14,66–72] and have reported conflicting findings. Some of these studies reported an association between VI and the development of depression[10,14,69,70] while others did not.[66–68,71,72] Further, only some of the very limited number of studies were population based[10,14,67–72].

Choi et al[14] found that those meeting the legal definition of VI had increased risks of depression at 11-years of follow-up in a Korean adult sample (n=29,230) after adjusting for age, sex, income, region of residence, hypertension, diabetes and hyperlipidemia (Hazard ratio (HR)=1.19, p=0.002). Study participants were identified using the Korean National Health Insurance Service and therefore those who had not sought clinical care for either VI or depression were excluded, severely limiting the generalizability of the results.

Harris et al[68] reported an association with self-declared poor vision and the onset of depression at 2-years of follow-up (adjusted OR=2.9, 95% CI=1.3-6.3) in a sample of 1164 adults aged >65 in two South London practices, after adjusting for age, sex, and practice . A major limitation of this study, however, was the use of a subjective measure of vision.

A study by *Hong et al*[69] found an increased odds of depressive symptoms (measured using the Mental Health Index questionnaire) or use of antidepressant medication(adjusted OR=3.06, 95% CI 1.72-5.44) among VI cases (defined as having best-corrected visual acuity worse than 20/40) detected 5-years earlier in a sample (n=1568) of Australian adults aged ≥49 after controlling for age, sex, walking disability, hospital admissions in the past 12 months, living arrangements, and comorbidity. This association was not seen at 10-years of follow-up (OR=1.29, 95% CI 0.84, 1.98).. These researchers did not appear to exclude those with depressive symptoms at baseline eliminating the benefit of having longitudinal data to establish the temporality.

Brown and Barrett[10] found that VI was a significant predictor of the development of depressive symptoms (measured using an abbreviated form of the CES-D scale) at 3-years of follow-up in an American population-based sample (n=1,221) of older adults (β=0.29, P=0.01). The measure of VI was based on self-report.

All but one of these studies were conducted outside of Canada and therefore these findings may not necessarily apply to the Canadian population due to differing healthcare and social environments. *Tournier et al*[70] conducted a study using provincial administrative health records of older adults aged ≥ 65 years from Quebec, Canada and reported an increased risk of depression among those with VI (HR:1.35, 95% CI 1.10-1.66 for severe VI, HR: 1.35, 95% CI 1.09-

1.69 for moderate VI) after adjusting for age, gender, chronic disease score, fracture and diabetes. VI was defined using ICD-9 diagnosis codes, which have unknown validity. Furthermore, as the study sample was limited to a single province**,** these results may not be generalizable to the general Canadian population. Further, the outcome of incident depression was defined as incident antidepressant medicationuse or a new diagnosis of depression which would exclude those who have not sought treatment thereby causing misclassification.

In contrast, several studies did not find an association. *Prince et al*[71] found that self-reported eyesight problems were not a risk factor for the onset of depression at one-year of follow-up in a population-based older adult sample (n=889), aged ≥ 65 years, from London UK. *Forsell et al*[67] reported that VI was not associated with a physician diagnosis of depression according to DSM-IV at 3-years of follow-up in a sample (n=894) of elderly adults aged ≥75 years in Stockholm, Sweden. *Heesterbeek et al*[66] found no association with VI and the development of depression (measured using the CES-D scale) at 2-years of follow-up in an outpatient sample of Dutch older adults aged ≥ 50 years using a linear mixed model. They did, however, find an association between AMD and the incidence of depressive symptoms at 2-years (β=0.12, 95% CI 0.04, 0.21). *Zheng et al*[72] found that baseline best-corrected visual acuity was not associated with the development of depressive symptoms (measured using the depression subscale of General Health Questionnaire 28) in a sample of 2520 older adults aged 65-84 using data from the Salisbury Eye Evaluation. They also reported that visual acuity at baseline was not associated with worsening depressive symptoms but that depressive symptoms at baseline were associated with worsening visual acuity over time. This indicates that some of the cross-sectional associations may be due to reverse causality.

Several of these studies utilized older adult samples[67,70,71] in which eye disease and VI were more likely to be identified due to more frequent medical visits in these populations and therefore study results may not be generalizable to younger age groups. Besides VI, other risk factors for the development of depression that were identified in these longitudinal studies include: disability or disablement[68,69,71], particularly handicap[71]; social isolation[68,71]; a history of depression/anxiety[66–68]; financial vulnerability[66,68]; living alone, having AMD[66]; poor physical health, stressful life events, comprised social support, increasing age[68]; and female sex[69].

Potential Causal Pathways

The identification of intervening variables in the causal pathway can shed light on aetiology and can provide additional targets for intervention. The loss of vision late in life can make it difficult to participate in fulfilling lifestyle activities. It has been reported that participation in a wide variety of lifestyle activities is associated with reduced levels of depressive symptoms[73–75] and that the social and psychological benefits obtained through the participation in a variety of activities may prevent the onset of MDD[76]. For instance, *Parisi et al*[77] found that greater participation by older adults in creative activities was protective against incident depression (HR=0.92, 95% CI 0.87, 0.98). As it may be more difficult for people with eye diseases and VI to participate in a greater variety of lifestyle activities due to their functional impairments, it may increase their risk of developing depressive symptoms. For example, results from a cross-sectional hospital-based study in Montreal, Canada found that older adults with AMD and glaucoma participated in fewer cognitive activities as compared to those with normal vision.[78] Another potential intervening variable, or mediator, may include reductions in IADLs[79]. IADLs

are functional abilities and include activities such as laundry, housekeeping, transportation, cooking, and managing finances.

A previous cross-sectional study examined whether a measure of mobility called life space and activity limitation due to a fear of falling acted as mediators of the relationship between age-related eye disease and depression. It found some evidence that both of these variables acted as mediators but mediation really requires multiple waves of longitudinal data to properly investigate it[80].

Cognitive Function

Cognition is defined as the processes carried out by the brain (including the ability to learn, problem solve, remember and appropriately use stored information[81]) by which an individual becomes aware of their situational needs and required actions[82]. Small declines in cognitive abilities (including processing speed, memory, language, and executive function) are associated with the normal aging process (due to structural and functional brain changes including declines in grey and white matter volume, and neurotransmitter levels) and do not result in functional impairment[83]. A diagnosis of dementia is typically made when the acquired level of cognitive decline exceeds the levels seen in healthy cognitive aging and compromises an individuals' social and/or occupational functioning[84].

Mild cognitive impairment (MCI) is an intermediate state of cognitive ability, between normal cognition and dementia, in which functional abilities are essentially preserved[84]. The *DSM-V* diagnosis of MCI is made when modest impairment in one or more cognitive domains (complex attention, executive functioning, learning and memory, language, perceptuomotor functioning, and social cognition) is present but there is no interference with the individuals'

independence in everyday activities, albeit these activities may require more time, effort, accommodation or compensatory strategies[28]. Further, the cognitive deficits must not occur exclusively during delirium or be better explained by another mental disorder[28].

In older adults, impaired cognition and reduced cognitive abilities can occur due to neurodegenerative, vascular, and dysthymia/dysphoria related factors[85]. The prevalence of MCI among older adults is estimated at 6-26%[86,87]; however, the reported prevalence rates in studies vary greatly due to the use of different diagnostic tests and cut-off scores in defining MCI, age at initial assessment and length of follow-up[88]. Around 46% of individuals diagnosed with MCI develop dementia within 3 years as compared to 3% among individuals of the same age without a diagnosis of MCI[89].

Cognitive impairment is frequently assessed in research by using screening tests such as the Mini-Mental-State-Examination[90] and the Clock Drawing Test[91]. Many of the commonly used screening tests rely on vision, which is very problematic. Visually impaired people can have perfectly normal cognition but fail a cognitive test because they cannot see the test well or they are slower at completing the test. One solution is to omit the visual items [92–95] although the cognitive test would need to be re-validated. A better approach is to use tests that are orally administered such as the Rey Auditory Verbal Learning Test (RAVLT) [96], the Controlled Oral Word Association Test (COWAT)[97] and the Animal Naming Test (ANT)[98].This approach ensures accurate diagnosis and equal access to treatment in those with VI[99].

Current treatment practices

There are no specific treatments recommended for MCI; individuals are encouraged to present early with memory problems to ensure diagnosis and care are planned at an early stage[100]. Systematic reviews of randomised controlled trials assessing the efficacy of pharmacological treatments for MCI found marginal beneficial effects of all cholinesterase inhibitors[101], doneprezil[102] and galantamine[103], which were outweighed by the risk of adverse events. Among individuals with MCI, targeted treatments including neuroprotection, treating vascular risk factors and increasing cognitive reserves could delay the decline in cognitive function in those at high risk of developing dementia[100].

Risk factors for MCI

Regular physical activity and management of cardiovascular risk factors including diabetes, obesity, smoking and hypertension reduce the risk of cognitive decline[104]. Other factors that have been found to be associated with a lower risk for cognitive decline include involvement in cognitive, physical, or other leisure activities and dietary factors such as a Mediterranean diet, vegetable and ω-3 fatty acid intake[105].

Diabetes

Several studies have shown lower cognitive performance among individuals with diabetes[104–107]. Further, individuals with MCI and diabetes were found to be more likely to progress to dementia than individuals with MCI and no diabetes[107], with evidence suggesting this increased risk occurs through vascular pathways and interactions of other biological mechanisms related to the diabetes disease process[108,109].

Obesity

Previous research has provided evidence that obesity in the mid-life is associated with an increased risk for decline in cognitive function and may be more detrimental to subsequent age-related cognitive decline than being overweight or obese at later stages of the lifespan[110–113].

Lifestyle risk factors

There is strong evidence that current smoking increases the risk of cognitive decline[105,114,115]. Sleep disturbances including insomnia and sleep apnea have also been shown to be associated with increased risk for cognitive decline among older adults[117–119].

Various other lifestyle-related factors have been identified to be associated with a decreased risk of cognitive decline among older adults; these include physical activity[114,120–122], a Mediterranean diet[123,124], small or moderate alcohol consumption[125,126], participation in social activities and larger social networks[127,128], more years of formal education and greater literacy[120,129,130].

Visual Impairment, eye disease & cognitive decline

Hypotheses linking vision, eye disease, and cognitive decline:

Various hypotheses exist about why vision/eye disease and cognition may be related. First, the Common Cause hypothesis, contends that vision and cognitive declines are both part of brain aging and share no direct relation; rather there exists a third factor common to vision and cognition such as biological pathways or other risk factors[131]. For example, specific visual

disorders like AMD and glaucoma have been shown to share common pathogenic pathways with Alzheimer's disease including glial reactivity, neuroinflammation, and oxidative stress[132].

Second, the Sensory Deprivation, also called the Disuse hypothesis, is that the reduction in physically and mentally stimulating activities resulting from low vision, in turn, increases the risk of further declines in cognitive function[131,133,134]. For example, past research has reported that participating in more cognitive activities is associated with reduced risks of developing dementia[135,136] and therefore eye disease may increase the risk of cognitive decline by affecting intervening variables on the causal pathway.

Cross-sectional study findings:

Findings from cross-sectional studies have shown that VI[93,137–140] and age-related eye diseases including AMD[93] and diabetic retinopathy[140] are associated with cognitive impairment in older adults. Among older adults, cognitive impairment was also found to be associated with several risk factors including: increased age[93,137–140], less education[93,138–140], lower income[138,140], hypertension[93,137,140], diabetes mellitus[93,137,138], hearing loss[137,139], a higher number of chronic conditions[139], and current smoking status[93].

Longitudinal study findings:

Of the limited number of longitudinal studies that have examined the possible associations of VI or age-related eye disease with subsequent cognitive decline, five studies[141–145] found that VI was longitudinally associated with a decline in cognitive function and one study reported no significant associations[146].

For example, Hong et al[146] performed a prospective, population-based study of 3,654 participants of the Australian Blue Mountains Eye Study to assess whether VI was associated with a decline in MMSE scores over 10 years. After adjusting for age and sex, VI was not associated with cognitive decline over 5 years (OR 0.84; 95% CI 0.40-1.79) or 10 years (OR=1.09; 95% CI 0.52-2.30). Possible cognitive decline was defined as change ≥3 from 5-year to 10- or 15-year visits on the visually dependent MMSE test, which limits the accuracy of the diagnosis, especially among those with impaired vision.

Zheng et al[141] evaluated the longitudinal associations between VI and cognitive function using cross-lagged models for a population-based sample (n=2,520) of older adults aged 65-84 years in Salisbury, Maryland. After adjusting for age, sex, race and education they reported that VI measured at a distance was associated with declining cognitive function (β = -0.074; SE, 0.015; P < .001). A limitation to this study is the use of the visually dependent MMSE test as a measure of cognitive function. The authors tried to account for this by omitting the vision-dependent items in those whose vision was worse than 20/30 and then prorate their score to be comparable to the full MMSE test. However, the validity of this approach is not known.

Lin et al[147] assessed the association between VI and subsequent cognitive decline in community-residing older women (n=6,112) from four metropolitan areas of the United States. They found that VI at baseline was associated with cognitive decline (OR= 1.78, 95% CI: 1.21-2.61) after adjusting for medical comorbidities, age, education, smoking, vertebral fracture, benzodiazepine use, BMI, Lubben social network, grip strength, walking speed, and baseline cognitive status. However, as cognitive decline was defined as an amount of decline from baseline to follow-up that exceeded the observed average change in 3MS test scores by at least

one standard deviation, the generalizability of these study findings to other patient populations remains unknown. Furthermore, the 3MS contains items that require vision, which could create a spurious association with VI because of an unfair testing disadvantage.

Swenor et al[143] assessed the association between VI and cognitive outcomes using multiple measures of vision (visual acuity (VA), contrast sensitivity, and stereo acuity) in a sample of community-dwelling, older adults (n= 3,075) aged 70-79 years, residing in Pittsburgh, Pennsylvania or Memphis, Tennessee. Using linear mixed effects models they found that VA (HR=1.55; 95% CI 1.12-2.14), contrast sensitivity (HR=1.33; 95% CO 1.13-1.55) and stereo acuity (HR= 1.28 1.09-1.49) impairments were associated with greater declines in the 3MS scores over 9 years after adjusting for year, age, sex, race, education, smoking, depression, diabetes, study site and interaction terms between the vision parameters and years in study. Again, this study used the 3MS which unfairly penalizes people with vision loss.

Lim et al[144] assessed the association between VI and decline in cognitive function over 6 years in a multi-ethnic Asian population (n=2,478) aged 60+ recruited from the Singapore Epidemiology of Eye Diseases Study. VI at baseline was found to be associated with a decrease in Abbreviated Mental Test score over 6 years (β = −0.27; 95% CI, −0.37 to −0.17; $P < .001$) after adjusting for age, sex, race/ethnicity, presence of diabetes, hyperlipidemia, hypertension, chronic kidney disease, history of cardiovascular disease, smoking status, alcohol intake, BMI, educational status, and baseline AMT score.

Finally, Effendi-Tenang et al[145] evaluated the longitudinal association of VI with cognitive decline using data from the Malaysian Elders Longitudinal Research study of adults aged 55+ (n=1144). They reported that among those who had greater than 6 years of education attainment, VI was associated with a reduction on Montreal Cognitive Assessment (MoCA)-blind test scores after adjusting for age and gender ((β = 1.86; 95% CI, 1.08 to −3.21; *P* = 0.025). However, this study utilized a modified version of the MoCA test in which visual-related items were removed thereby reducing its sensitivity.

Potential causal pathways

One of the most effective prevention mechanisms against cognitive decline is increasing brain and cognitive reserve capacity[148]. Behavioural activities have recently shown potential in improving cognitive abilities by inducing neuroplasticity within the brain via increasing synaptic and dendritic receptors and changes in neuronal growth factors[149,150]. Studies have found participation in social and leisure activities by older adults to be associated with a decreased risk of cognitive decline[151,152]. The loss of vision experienced among those with VI and age-related eye disease may hinder performance on mentally stimulating activities and result in behavioural changes and decline in cognitive function.

For example, a growing body of evidence suggests that participation in cognitive[136,153,154], physical[155], and social activities[152] and in IADLs[156,157] among older adults leads to a slower decline in cognitive function by enhancing cognitive reserve.[158,159]

Thesis rationale

As such, data from the CLSA Comprehensive Cohort will be used to examine the longitudinal association between an objective measure of VA with cognitive decline and a validated measure of incident depression in community-dwelling older adults. We will also examine the association between the self-report of macular degeneration, glaucoma, and cataract with incident depression or cognitive decline. We will be examining data on over 30,000 participants over a 3-year period, which will enable us to rigorously assess temporality and risk factors of developing depression or cognitive decline among those with age-related eye disease and VI.

In addition, by examining the Canadian-specific consequences of age-related eye disease and VI, we will provide data useful for others to examine the indirect costs of vision loss. Our project will provide novel data, which will assist in the identification of groups with increased risks, and may lead to the development of novel interventions to prevent these potentially adverse consequences from developing in the first place.

CHAPTER 3: RESEARCH AIMS

Aim 1. Determine whether baseline visual impairment or eye disease is associated with the 3-year change in cognitive scores.

Sub-aim 1.1. Assess whether sex, education or hearing loss act as effect modifiers of the association between vision-related variables and 3-year changes in cognitive scores.

Aim 2. Determine whether baseline visual impairment or eye disease is associated with the 3-year incidence of depression.

Sub-aim 2.1. Assess whether sex, education or hearing loss act as effect modifiers of the association between vision-related variables and incident depression.

CONCEPTUAL FRAMEWORK

The conceptual framework used to formulate aims 1 and 2 and guide data analysis is presented in Figure 1. The relationships between baseline VI or eye disease and cognitive decline and incident depression may be confounded by factors such as age, sex, education, ethnicity, income, tobacco consumption, and by the presence of comorbid conditions. For example, Zheng *et al.*[141] found that age, sex, race and education were confounders of the association between VI and declining cognitive function in a US popultion-based sample of older adults.

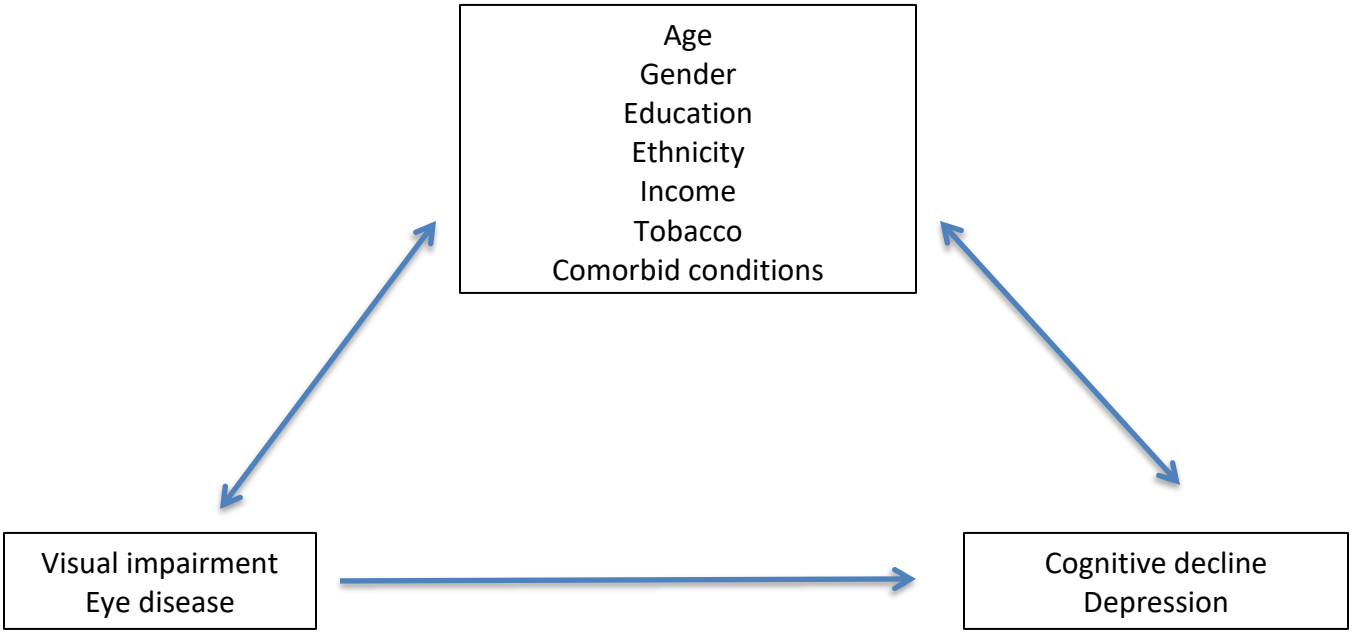

Figure 1. Conceptual framework for aims 1 and 2 of the project

Further, effect modification will be tested by adding two variable product terms of the vision-related variables (VI, AMD, glaucoma, cataract) X (hearing, sex, education) into regression models. These three variables were chosen for a combination of conceptual and practical reasons. Hearing impairment is known to be associated with both outcomes[160,161].

Those with lower education might be at a greater risk from vision loss due to less knowledge of how to advocate for themselves within the healthcare system. Further, the lower socioeconomic status, less effective coping mechanisms and unhealthier lifestyles associated with lower education levels[162,163] could lead to increased risks for depression and cognitive decline. Women are known to be at a higher risk of depression[51,54]. Finally, these three exposures are common enough to give reasonable sample size to examine interaction.

CHAPTER 4: METHODS

Study Design and Population

A prospective analysis was performed using data from waves 1 and 2 of the Canadian Longitudinal Study on Aging (CLSA) Comprehensive Cohort consisting of 30,097 individuals at baseline. The CLSA cohort was recruited using three methods: i) a subset of participants in the Canadian Community Health Survey- Healthy Aging (CCHS); ii) provincial health care registries; and iii) random digit dialing of landline telephones. The overall response rate into the CLSA was 10%. Participants in the Comprehensive Cohort underwent a baseline physical assessment including a visual acuity test, central to this study. Baseline data were obtained via in-home interviews and data collection site visits between 2010 and 2015. Core information on demographic and lifestyle/behaviour, social, physical/clinical, psychological, economic, and health status measures, as well as health service use were collected via 70-minute-in-home interviews. Baseline in-home interviews consisted of two parts, informed consent and administration of the questionnaire. Participants recruited to the Comprehensive Cohort were also asked to visit a CLSA data collection site within 25-50km of their home within 2-3 weeks of the in-home interview to undergo detailed physical assessments. The 11 data collection sites are located in Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montreal, Sherbrooke, Halifax and St. John's at CLSA-affiliated universities.

To be included in the study, participants had to be aged between 45 and 85 years, community dwelling, cognitively unimpaired, and speak English or French. Exclusion criteria included being a full-time member of the Canadian Armed Forces, residing on a federal First

Nations reserve or settlement, living in a long-term care institution, or not a permanent resident or Canadian citizen.

The 3-year follow-up data were obtained between June 2015 and May 2018. Data for the core information set was collected via in-home interviews and detailed physical assessments took place at CLSA data collection sites. Participants aged greater than 70 years at baseline were asked to provide the name of a proxy decision maker and proxy information provider in the case participants became unable to participate on their own. Reasons for participant attrition at 3-years of follow-up including losses to follow-up, deaths and refusals to continue in the study were obtained via linkages with mortality databases and contact with alternate contacts identified at baseline.

Ethics Approval and Data Access:

The CLSA submitted a full-integrated protocol, including the Comprehensive Cohort protocol, in July 2010 to the affiliated universities and REB approval was received. Ethical approval for the present analysis was obtained from the University of Ottawa in May 2019.

Power Calculations

PS Power and Sample Size software (Version 3, Dupont and Plummer) was used to calculate power for our research aims.

With a baseline prevalence of VI of 5.7%, we had 80% power to detect an odds ratio as low as 1.24 with an incidence of depression of 7.7%, as we saw, assuming 27,412 people, and a Type 1 error rate of 5%.

We had 80% power to detect a difference of 0.125 or greater in RAVLT scores between the groups with and without VI assuming a standard deviation of 1.9, 27,412 people, and a Type 1 error rate of 5%. The other minimum detectable differences were 0.135 for changes in the RAVLT delayed score, 0.530 for the COWAT, 0.640 for the ANT, and 0.43 for the MAT.

CHAPTER 5: MANUSCRIPTS

Cover Page

Manuscript #1 of the thesis follows. This manuscript has been accepted for publication at the journal Ophthalmic Epidemiology.

Visual impairment, eye disease, and the 3-year incidence of depression:

The Canadian Longitudinal Study on Aging

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ABSTRACT

Objectives: Our goal was to explore the longitudinal association between vision-related variables and incident depression in a community-dwelling sample of older adults and to examine whether sex, education, or hearing loss act as effect modifiers.

Methods: A 3-year prospective cohort study was performed using data from the Canadian Longitudinal Study on Aging consisting of 30,097 individuals aged 45-85 years. Visual impairment was defined as binocular presenting visual acuity worse than 20/40. Incident depression was defined using a cut-off score of 10 or greater on the Center for Epidemiologic Studies Depression scale in those who did not have depression at baseline. Participants were asked if they had ever had a physician diagnosis of age-related macular degeneration (AMD), glaucoma, or cataract. Multivariable Poisson regression was used with vision-related variables entered into separate models. Sampling weights were included.

Results: Of 22,558 participants without depression at baseline, 7.7% developed depression within 3 years. Cataract was associated with incident depression (relative risk=1.20, 95% confidence interval 1.05, 1.37) after adjusting for age, sex, income, education, partner status, smoking, level of comorbidity, and province. Visual impairment, AMD, and glaucoma were not associated with incident depression. No effect modification was detected.

Conclusions: These are the first longitudinal data to indicate that the risk of depression is higher in those who report ever having a cataract. Further research should confirm our finding and should determine if the increased risk is primarily in those who have already had surgery or those who are waiting for surgery.

Keywords: Visual impairment, Age-related eye disease, Canadian Longitudinal Study on Aging, Depression

Introduction

Vision loss is very common in old age due to uncorrected refractive error and age-related eye diseases like cataract, age-related macular degeneration, glaucoma, and diabetic retinopathy (1). Some older adults are able to adapt well to vision loss adopting a resilient attitude and positive coping skills. However, other older adults struggle to accept and adapt to their vision loss and are at risk of depression (2).

Many cross-sectional studies have identified a relationship between visual impairment or eye disease and depression (3-8). However, cross-sectional studies are limited because they cannot establish temporality of the vision loss and the onset of depression. As such, they cannot rule out reverse causality such that depression might aggravate the proper care for vision problems thereby exacerbating vision loss. Some longitudinal studies, which can establish temporality, have been done although the results are somewhat conflicting (9-13). Furthermore, few of the longitudinal studies have examined effect modifiers to indicate whether some groups of people are at a greater risk of depression after losing vision than others. One cross-sectional study that did examine effect modification found that people with cataract and lower education had a higher prevalence of depressive symptoms than those with cataract and higher education (7). Other differences might be seen by sex or the loss an additional sensory system like hearing.

The Canadian Longitudinal Study on Aging is a large, population-based cohort study with data on over 30,000 middle-aged and older adults (14). We utilized this dataset to examine the association between visual impairment or eye disease and the 3-year incidence of depression and to determine whether sex, education, or hearing loss modifies any of the associations.

METHODS

Study Population

A prospective study of community-dwelling older adults was performed using data from rounds 1 and 2 of the Canadian Longitudinal Study on Aging (CLSA) Comprehensive cohort consisting of 30,097 individuals (14). The sampling strategy used in the CLSA Comprehensive cohort consisted of provincial healthcare registration databases and random digit dialing of landline telephones. Stratified random sampling was used to ensure participants met the specified demographic distributions (i.e. age, sex, urban-rural) required from each province. To be able to participate, participants had to be aged between 45 and 85 years, community-dwelling, cognitively unimpaired at baseline, speak English or French, and provide written informed consent. Exclusion criteria included being a full-time member of the Canadian Armed Forces, residing on a federal First Nations reserve or settlement, living in a long-term care institution, or not being a permanent resident or Canadian citizen.

STUDY DESIGN

The baseline assessment included a home visit and a data collection site visit done between December 2011 and July 2015. The 11 data collection sites are located in Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montreal, Sherbrooke, Halifax and St. John's. All CLSA Comprehensive Cohort study personnel received standardized training on data collection procedures in order to ensure that participant assessments were standardized across the data collection sites. Follow-up data were obtained between July 2015 and December 2018 in a home visit and a visit to a data collection site. The follow-up rate was very high at 92%. Research Ethics Board approval was received in July 2010 from all affiliated sites. Ethics approval from the University of Ottawa was received for the present analysis in May 2019.

DATA COLLECTION

Visual Impairment and Eye Disease

Baseline visual acuity was measured by trained study personnel at the data collection site using an illuminated Early Treatment of Diabetic Retinopathy Study (ETDRS) chart and its standard protocol (15). Visual acuity was evaluated at a 2-meter distance from the letter chart using habitual distance correction (i.e. wearing normal corrective lenses for distance vision). Acuity scores from participants were converted to logMAR units. Baseline visual impairment was defined as presenting binocular acuity worse than 20/40 (0.301 logMAR), as is standard in North American studies (16). Participants were asked if a doctor has ever told them that they have or had cataract, macular degeneration, or glaucoma.

Depression

The Center for Epidemiologic Studies Depression scale (CES-D10) was used to measure depressive symptomatology (17). The CES-D10 consists of 10 items covering depressive symptomatology experienced during the past week and includes 4 response categories ranging from "rarely" to "all of the time". The instrument takes approximately three minutes to administer; scores range from 0-30 with a score of 10 or greater indicating that a participant has screened positive for depression. Incident depression was present in those who had a score of 10 or higher at follow-up in those who scored less than 10 at baseline.

Demographic, Health, and Lifestyle Data

Demographic data including age, sex, education, income, and marital status were collected at baseline during the in-home visit using the interviewer-administered questionnaire. Participant education level was determined by asking, "What is the highest degree, certificate or diploma you have obtained?". In order to assess household income, participants were asked, "What is your best estimate of the total household income received by all household members,

from all sources, before taxes and deductions, in the past 12 months?". Self-reported marital status was dichotomized into partnered (married/living with a partner) and not partnered (single, never married or lived with a partner, widowed, divorced, or separated).

Regarding health, hearing was assessed by asking participants, "Is your hearing, using a hearing aid if you use one, excellent, very good, fair or poor?". For use in our analyses, participant responses were dichotomized into two categories: good, very good, or excellent versus fair or poor. Participants were asked if they had ever received a physician diagnosis of 9 chronic conditions which included diabetes, heart disease, stroke, osteoarthritis of the knee or hip, peripheral vascular disease, asthma, back problems, and Parkinson's disease. As is often done in aging research, a comorbidity score was created based on the total number of the 9 chronic conditions listed above. Scores range from 0-9, with higher scores reflecting a greater number of chronic conditions present among participants.

Smoking status was classified as either current, never, or former based on participant responses to the interview questions "Have you smoked at least 100 cigarettes in your life?" and "At the present time, do you smoke cigarettes daily, occasionally (at least once in last 30 days), or not at all (not in last 30 days)?". A current smoker was defined as a person who reported smoking at least 100 cigarettes and currently smokes daily or occasionally while a former smoker was someone who reported smoking at least 100 cigarettes in life but had not smoked in the last 30 days.

Statistical Analysis

Those with and without incident depression were compared for visual, demographic, health, and lifestyle factors at baseline. Multiple Poisson regression was used to assess the association of vision-related variables at baseline with incident depression adjusting for potential

confounding variables including age, sex, household income, level of education, marital status, smoking status, number of chronic conditions, and province. These variables were chosen based on previous research showing their importance to vision or depression (9, 10). Given prior reports of a nonlinear relationship between age and depression (18), age was modeled both linearly and nonlinearly while examining Akaike's information criteria to determine the optimal fit to the data. Effect modification was tested by adding product terms into regression models. Statistical significance was considered to be $P < 0.05$. As recommended by the CLSA, sampling weights and strata variables were incorporated into all analyses. This was done using the SVY commands in STATA SE Version 16 (College Station, Texas).

RESULTS

Descriptive

Of the 27,643 out of 30,097 who returned to follow-up after 3 years (92%), 23,451 did not have depression at baseline and were therefore eligible for the development of incident depression. Our analysis consisted of 22,558 people after excluding those who were missing depression data at follow-up. Of the 2,454 who did not return to follow-up, 974 died (40%) and 967 withdrew (39%) with the remaining 513 (21%) either unable to be contacted or unable to complete data collection. Participants who were lost to follow-up were older, had lower education, lower household income, were more likely to smoke, to be unpartnered, and had higher comorbidity scores compared to those with who were not lost to follow-up.

Of the 22,558 in our analysis cohort, the mean age of participants, after correction for the complex survey design, was 59.2 years (SD=9.6) and 49.0% were female. Overall, at baseline, 5.1% of participants in the cohort had VI, 20.2% reported ever having had a cataract diagnosis, 2.8% reported a diagnosis of macular degeneration, and 3.6% reported a diagnosis of glaucoma.

Baseline characteristics of the cohort by depression status are presented in Table 1. The incidence of depression was 7.7% after accounting for the complex survey design. Those who developed depressive symptoms were more likely to report a previous diagnosis of cataract, AMD, and glaucoma, were older, more likely to be female, had lower levels of education, lower total household incomes, were more likely to be current smokers, unpartnered, and had higher levels of comorbidity compared to those who did not develop depressive symptoms.

Visual Impairment and Depression

As shown in Table 2, visual impairment was not associated with incident depression after adjustment (relative risk (RR)=0.94, 95% CI 0.76,1.17). No interactions were found with sex, education, or hearing loss. Factors that were associated with a higher risk of incident depression included female sex (RR=1.49, 95% CI 1.34, 1.67), lower household income (e.g. RR=2.22, 95% CI 1.71, 2.88) for those earning less than $20,000 per year, lower education levels (RR=1.19, 95% CI 1.03, 1.39) for those with less than a Bachelor's degree, current smoking (RR=1.62, 95% CI 1.136, 1.93), and higher levels of comorbidity (RR=1.31, 95% CI 1.25, 1.37). Pinhole corrected visual impairment in the better eye was also not associated with incident depression (RR=1.00, 95% CI 0.78, 1.28).

Age-Related Eye Disease and Depression

Having or having had cataract was associated with an increased risk of becoming depressed after adjustment (RR=1.20, 95% CI 1.05, 1.37) (Table 3). Adjusting for presenting binocular visual acuity did not alter the relationship between cataract and incident depression (RR=1.24, 95% CI 1.09, 1.41). By contrast, AMD was not associated with an increased risk of becoming depressed (RR=1.21, 95% CI 0.97, 1.53) after adjustment for demographic, lifestyle, and health variables (Table 4) nor was there a statistically significant relationship between a self-

report of glaucoma and the incidence of depression (RR=1.10, 95% CI= 0.89, 1.36). No interactions were found between eye disease and sex, education, or hearing loss.

DISCUSSION

We did not find that visual impairment, defined using presenting acuity or pinhole-corrected acuity, or that the self-report of AMD or glaucoma increased the 3-year risk of incident depression. However, we did find that the self-report of a diagnosis of cataract was related to incident depression. The relationship with cataract was unaltered by adjusting for visual acuity indicating the association is primarily explained by other unknown factors.

To our knowledge, our results are the first to demonstrate a longitudinal relationship between a prior diagnosis of cataract and incident depression. Cataract is a treatable condition. It is unclear if our association is found primarily in those who currently have a cataract in the eye or rather just in those who have already had surgery or in both groups equally. Two cross-sectional papers support our findings. Eramudugola *et al* found that the self-report of having or having had a cataract was associated with greater depressive symptoms (OR=1.40, 95% CI 1.07, 1.81) (8). Wang *et al* found that currently having a cataract in the eye, as measured using the Lens Opacities Classification System III scheme, was associated with depressive symptoms (OR=1.33, 95% CI 1.08, 1.70) despite adjusting for presenting visual acuity (7). Cataract-related factors besides visual acuity that might affect depression include difficulty with glare sensitivity or contrast sensitivity, fear of cataract surgery, difficulty doing visual tasks, or complications with obtaining surgery such as long wait times or uncovered surgical costs. The stress from cataract may serve as a "tipping point" for some people so that even when the cataracts are removed, the depression does not subside (19). There may additionally be stress related to

postoperative treatment recommendations and possible surgical complications. Furthermore, Wang *et al* identified an interaction such that the association between cataract and depression was even stronger in those with lower education (P-value for interaction = 0.03) (7). We did not find an interaction between cataract and education in the CLSA data nor did we find any interactions with sex or hearing loss.

As noted, we did not find that visual impairment was associated with incident depression. Our results are in agreement with five prior longitudinal studies which found visual impairment and self-reported sight problems were not associated with the onset of depression (9, 20-23). The most comprehensive examination was by Zheng *et al* who used latent growth curve modeling to examine 4 rounds of data from the Salisbury Eye Evaluation. They found, similar to us, that visual acuity at baseline was not associated with worsening depressive symptoms although it was associated with baseline depressive symptoms. They also found that depressive symptoms at baseline were associated with worsening visual acuity over time indicating that reverse causality could be at least partially driving cross-sectional associations. The mechanism for this association could be that depression may lead to worse compliance with recommended treatment regimens for eye conditions (24, 25).

Our results are in contrast to four past studies that found visual impairment to be associated with incident depression (10). For example, in Australia, Hong *et al* found that people with best-corrected visual acuity worse than 6/12 had a higher 5-year odds of incident depression using a questionnaire called the Mental Health Index (OR=3.06, 95% CI 1.72, 5.44) although they did not see an association at 10 years (OR=1.29, 95% CI 0.84, 1.98) (10). Brown and Barrett found that visual impairment was a significant predictor of an increase in depressive symptoms over 3-years of follow-up in an American cohort of 1,221 people from the 1980's

(β=0.29, P=0.01) (26). In a retrospective cohort study of 21,995 people using Quebec health administrative records, Tournier *et al* found that a diagnosis of moderate or severe visual impairment was associated with a higher adjusted risk of incident depression after excluding those with a history of depression in the two years prior to the index date (hazard ratio (HR)=1.38, 95% CI 1.25, 1.91 for blindness or severe visual impairment and HR=1.30, 95% CI 1.18, 1.44 for moderate visual impairment) (11). Finally, in a retrospective cohort study of people enrolled in the Korean National Health Insurance Service, Choi *et al* found that those people meeting the legal definition of visual impairment had increased risks of a diagnosis of depression after adjusting for potential confounding factors (Hazard ratio (HR)= 1.19, P=0.002) (27). As these last two studies relied on diagnosis codes, those people with visual impairment or depression who had not sought clinical care were not included. The validity of the diagnosis codes for visual impairment and depression is not known.

Our finding that AMD was not related to the incidence of depression was not in agreement with two prior longitudinal studies. A 2-year prospective cohort study of low vision rehabilitation patients by Heesterbeek *et al* indicated that AMD was associated with the incidence of depressive symptoms using a linear mixed model (β=0.12, 95% CI 0.04, 0.21) while visual acuity was not (22). Also, a U.S. study by Wysong *et al* using Medicare claims data found an association between AMD and the incidence of depression, although the effect size was extremely small and perhaps not clinically significant (HR=1.06, 95% CI 1.02, 1.09) (13). We must note that when we adjusted for age in a linear fashion, AMD was associated with incident depression in our data. However, we found that age was non-linearly associated with incident depression and thus modeling age as a linear term would have led to residual confounding and

did not fit the data as well. Heesterbeek *et al* modeled age in a non-linear fashion while Wysong *et al* modeled age in a linear fashion.

We did not find a statistically significant relationship between glaucoma and the incidence of depression. Most studies assessing the association between glaucoma and depression were cross-sectional, utilized small sample sizes, and were conducted in hospital settings. One longitudinal study, a retrospective population-based cohort study conducted by Chen *et al* using the Taiwan National Health Insurance Research Database, reported conflicting findings to ours in that patients with glaucoma had a significantly higher risk of depression (adjusted HR=1.71, 95% CI 1.54-1.89) as compared to those without (12). Relying on medical records, as in Chen *et al*, or the use of the self-report of glaucoma, as we did, may result in misclassification since many people are undiagnosed (28).

A strength of this research was that this population-based, longitudinal dataset allowed us to measure the incidence of depression, to determine the temporality of the vision loss/eye disease and the onset of depression, and to adjust for a large number of potentially confounding variables. We appropriately modeled the non-linear relationship between age and incident depression and we examined potential effect modification. A limitation of this work is the use of self-reported data on the presence of eye disease. In particular, we are unable to determine which people who reported cataract had had cataract surgery because of substantial missing data for that question (57% missing). Also, survivor bias is always possible when doing aging research if the relationship between vision loss and depression is different in those who did not participate. We are reassured that the 3-year incidence of depression in those 65 and older in the CLSA (9%) is similar to the 3-year incidence of depression in NuAge, a population-based study of adults ages 65 and older in Quebec (12%) (29). Finally, our results may not be generalizable

to those excluded from the CLSA sampling frame which includes full-time members of the Canadian Armed Forces, those residing on a federal First Nations reserve or settlement, those living in a long-term care institution, those who are not a permanent resident or Canadian citizen, those not fluent in English or French, and those with cognitive impairment.

To summarize, these data indicate that the risk of depression is 20% higher in those who reported a previous diagnosis of cataract. Depression is a very common problem in the population with almost 8% of the population developing it within 3 years. Its presence may complicate efforts to treat eye disease (24, 25). Further research should confirm our finding and should determine if the increased risk is primarily in those who have already had surgery or those who are waiting for surgery. If confirmed, efforts should be made to address depression in those with cataract. Strategies to decrease depressive symptoms include greater screening and targeted interventions in high-risk groups (30, 31).

DATA AVAILABILITY

This research has been conducted using the CLSA Comprehensive Dataset version 4.0 and Follow-up 1 Comprehensive Dataset version 1.0 under Application Number 190212. The CLSA is led by Drs. Parminder Raina, Christina Wolfson, and Susan Kirkland. The opinions expressed in this manuscript are the author's own and do not reflect the views of the Canadian Longitudinal Study on Aging.

DISCLOSURE OF INTEREST

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Table 1. Descriptive statistics of those with and without incident depression

Variable	Depressed n= 1,807 Mean (SD)/Row %	Not Depressed n=20,751 Mean (SD)/Row %
Visually Impaired		
No	7.5	92.5
Yes	8.2	91.8
Cataract		
No	7.1	93.0
Yes	10.2	89.8
AMD		
No	7.6	92.4
Yes	11.1	88.9
Glaucoma		
No	7.6	92.4
Yes	9.8	90.2
Age Group, Years	60.0 (10.8)	59.1 (9.6)
45-55	7.6	92.4
55-65	6.9	93.1
65-75	7.1	92.9
75-85	11.4	88.6
Sex		
Female	9.5	90.5
Male	5.9	94.1
Education		
More than Bachelor's	5.9	94.1
Bachelor's	6.2	93.8
Less than Bachelor's	9.3	90.7
Annual Household Income		
≥ $150,000	5.7	94.3
$50,000 -$100,000	7.7	92.3
$20,000 - $50,000	11.1	88.9
<$20,000	18.6	81.4
Refused/ Don't know	10.0	90.0
Smoking		
Current	13.2	86.8
Former	7.6	92.4
Never	6.9	93.1
Marital Status		
Partnered	6.8	93.2
Not Partnered	11.1	88.9
Comorbidity Score	1.2 (1.1)	0.8 (0.9)

Table 2. Visual impairment and incident depression during the 3-year follow up

Characteristics	Adjusted RR*	95% CI
Visually impaired	0.94	0.76, 1.17
Age		
45-55	1.00	
55-65	0.80	0.70, 0.91
65-75	0.67	0.57, 0.78
75-85	1.02	0.86, 1.20
Female Sex	1.50	1.34, 1.67
Annual household income		
≥ $150,000	1.00	
$50,000 -$100,000	1.21	1.05, 1.39
$20,000 - $50,000	1.58	1.33, 1.89
<$20,000	2.22	1.71, 2.88
Refused/ Don't know	1.48	1.19, 1.85
Education		
More than bachelor's degree	1.00	
Bachelor's degree	0.97	0.82, 1.15
Less than Bachelor's degree	1.19	1.03, 1.39
Unpartnered Marital status	1.10	0.97, 1.25
Smoking status		
Never	1.00	
Former	1.04	0.93, 1.17
Current	1.62	1.36, 1.93
Comorbidity Score	1.31	1.25, 1.37

*Adjusted for all variables in table plus province and the complex survey design.

Table 3. Cataract and incident depression during the 3-year follow up

Characteristics	Adjusted RR*	95% CI
Cataract		
No	1.00	
Yes	1.20	1.05, 1.37
Age		
45-55	1.00	
55-65	0.78	0.68, 0.89
65-75	0.64	0.54, 0.75
75-85	0.89	0.74, 1.07
Annual household income		
≥ $150,000	1.00	
$50,000 -$100,000	1.21	1.05, 1.39
$20,000 - $50,000	1.57	1.31, 1.87
<$20,000	2.16	1.66, 2.80
Refused/ Don't know	1.47	1.18, 1.83
Education		
More than bachelor's degree	1.00	
Bachelor's degree	0.97	0.82, 1.15
Less than Bachelor's degree	1.19	1.03, 1.39
Unpartnered Marital status	1.10	0.97, 1.25
Smoking status		
Never	1.00	
Former	1.05	0.94, 1.18
Current	1.60	1.35, 1.90
Comorbidity Score	1.30	1.24, 1.36

*Adjusted for all variables in table plus province and the complex survey design.

Table 4. AMD and incident depression during the 3-year follow up

Characteristics	Adjusted RR*	95% CI
AMD	1.21	0.97, 1.53
Age		
45-55	1.00	
55-65	0.78	0.69, 0.90
65-75	0.67	0.58, 0.78
75-85	0.98	0.84, 1.16
Female Sex	1.48	1.33, 1.66
Annual household income		
≥ $150,000	1.00	
$50,000 -$100,000	1.21	1.05, 1.39
$20,000 - $50,000	1.56	1.31, 1.86
<$20,000	2.18	1.68, 2.82
Refused/ Don't know	1.44	1.16, 1.80
Education		
More than bachelor's degree	1.00	
Bachelor's degree	0.97	0.82, 1.15
Less than Bachelor's degree	1.20	1.04, 1.39
Unpartnered Marital status	1.10	0.98, 1.26
Smoking status		
Never	1.00	
Former	1.06	0.94, 1.18
Current	1.62	1.37, 1.93
Comorbidity Score	1.30	1.25, 1.36

*Adjusted for all variables in table plus province and the complex survey design.

Table 5. Glaucoma and incident depression during the 3-year follow up

Characteristics	Adjusted RR*	95% CI
Glaucoma	1.10	0.89, 1.36
Age		
45-55	1.00	
55-65	0.78	0.69, 0.90
65-75	0.68	0.59, 0.79
75-85	1.00	0.85, 1.17
Female Sex	1.49	1.33, 1.66
Annual household income		
≥ $150,000	1.00	
$50,000 -$100,000	1.21	1.05, 1.39
$20,000 - $50,000	1.55	1.30, 1.85
<$20,000	2.13	1.64, 2.76
Refused/ Don't know	1.46	1.17, 1.81
Education		
More than bachelor's degree	1.00	
Bachelor's degree	0.98	0.83, 1.16
Less than Bachelor's degree	1.21	1.05, 1.41
Unpartnered Marital status	1.11	0.98, 1.26
Smoking status		
Never	1.00	
Former	1.06	0.94, 1.18
Current	1.62	1.37, 1.93
Comorbidity Score	1.30	1.25, 1.36

*Adjusted for all variables in table plus province and the complex survey design.

COVER PAGE

Manuscript #2 follows. Due to several delays by the CLSA in releasing the data and then delays due to COVID-19, this manuscript is still in preparation for publication. Once completed, it will be submitted for publication although the target journal is still under consideration.

Visual impairment, eye disease, and the 3-year change in cognitive scores: The Canadian Longitudinal Study on Aging

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ABSTRACT

Objectives: Our goal was to explore the longitudinal association between vision-related variables and cognitive test change scores in a community-dwelling sample of older adults and to examine whether sex, education, or hearing loss act as effect modifiers.

Methods: A 3-year prospective cohort study was performed using data from the Canadian Longitudinal Study on Aging consisting of 30,097 individuals aged 45-85 years. Visual impairment (VI) was defined as binocular presenting visual acuity worse than 20/40. Participants were asked if they had ever had a physician diagnosis of age-related macular degeneration (AMD), glaucoma, or cataract. Cognitive change was examined by calculating the difference between baseline and follow-up scores of the Rey Auditory Verbal Learning Test (RAVLT), the Controlled Oral Word Association Test (COWAT), the Animal Naming Test (ANT) and the Mental Alternation Test (MAT). Multiple linear regression was used and sampling weights were included in all models.

Results: Visual impairment was associated with the 3-year change in RAVLT (β=-0.18, 95% confidence interval (CI)= -0.28, -0.07), RAVLT-Delayed (β=-0.13, 95% CI= -0.25, -0.02), and ANT (β=-0.95, 95% CI= -1.44, -0.45) scores after adjusting for age, sex, ethnicity, income, smoking, diabetes, stroke, heart disease, baseline cognitive score, and province. A report of glaucoma was associated with 3-year MAT change scores (β=-0.40, 95% CI -0.77, -0.04). The self-report of AMD or cataract were not associated with 3-year changes in cognitive test scores. No effect modification was detected.

Conclusions: These data indicate that VI and glaucoma are associated with 3-year changes in cognitive test change scores. Further research should confirm our finding and should examine potential pathways leading to the increased changes in cognitive function.

Keywords: Visual impairment, Age-related eye disease, Canadian Longitudinal Study on Aging, Cognitive Decline

Introduction

The loss of vision is very common in older age as 16% of adults aged 75-85 years old had visual impairment(1). A decline in cognitive function is also common in old age, which has led to substantial research to understand if the two are related(2–6). Theories about why the two might be related include that they share a common cause(7) or that the sensory loss itself causes disuse of the brain leading to atrophy(8–10).

Several longitudinal studies have indicated a relationship between visual impairment and cognitive function(11–16). However, many of them have a methodological flaw in that they used cognitive tests that rely on vision, which unfairly penalizes a person with vision loss(12,13,16). For example, the 3MS test requires that participants copy intersecting pentagons. A person with even minor vision loss, although able to do the test, may be slower or make more mistakes, not because of a cognitive problem but because they cannot see as well. Prior studies have also neglected to examine potential effect modifiers such as hearing loss, education, or sex. It may be that vision loss has a stronger relationship with cognitive decline in those with hearing loss, lower education, or by sex.

The Canadian Longitudinal Study on Aging is a large, population-based cohort study with data on over 30,000 middle-aged and older adults(17). We utilized this dataset to examine the association between visual impairment or eye disease and 3-year changes in cognitive test scores and to determine whether sex, education, or hearing loss modifies any of the associations.

METHODS

Study Population

A prospective study of community-dwelling older adults was performed using data from rounds 1 and 2 of the Canadian Longitudinal Study on Aging (CLSA) Comprehensive cohort consisting of 30,097 individuals(17). Stratified random sampling via the use of provincial healthcare registration databases and random digit dialling of landline telephones was done to ensure participants met the specified demographic distributions required from each province. To be able to participate, participants had to be aged between 45 and 85 years, community-dwelling, cognitively unimpaired at baseline, speak English or French, and provide written informed consent. Full-time members of the Canadian Armed Forces, individuals residing on a federal First Nations reserve or settlement, individuals living in a long-term care institution, or non-permanent residents and non-Canadian citizens were excluded.

STUDY DESIGN

Baseline and follow-up assessments included a home visit and a data collection site visit. All CLSA Comprehensive Cohort study personnel received standardized training on data collection procedures in order to ensure that participant assessments were standardized across the data collection sites. Baseline assessments were done between December 2011 and July 2015 and follow-up assessments were done between July 2015 and December 2018. The 11 CLSA data collection sites are located in Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montreal, Sherbrooke, Halifax and St. John's. The follow-up rate was 92%. Research Ethics Board approval was received in July 2010 from all affiliated sites. Ethics approval from the University of Ottawa was received for the present analysis in May 2019.

DATA COLLECTION

Visual Impairment and Eye Disease

Baseline visual acuity was measured at the data collection sites using an illuminated Early Treatment of Diabetic Retinopathy Study (ETDRS) chart and its standard protocol(18) and scores were converted to logMAR units. Visual acuity was evaluated at a 2-meter distance from the letter chart using habitual distance correction (i.e. wearing normal corrective lenses for distance vision). Baseline visual impairment was defined as presenting binocular acuity worse than 20/40 (0.301 logMAR), as is often done in in North American research(1). Participants were asked to report if they have or had a physician diagnosis of cataract, macular degeneration, or glaucoma.

Cognitive Change

Cognitive change was examined by calculating the difference between baseline and follow-up scores on validated non-visual cognitive tests including the Rey Auditory Verbal Learning Test (RAVLT) and the delayed-recall RAVLT trial (RAVLT-delayed) (19), the Controlled Oral Word Association Test (COWAT) (20), the Animal Naming test (ANT) (21), and the Mental Alternation Test (MAT) (22). Tests were administered in-person at study site visits by trained interviewers. These tests are reliable and widely used in neuropsychology to indicate cognitive decline(23,24).

During the RAVLT, a 15-item list of words was read to participants at a rate of one word per second. After presentation of the 15 words, participants were requested to recall as many words as possible. Records were kept of the words recalled and the order in which the participant said them. The procedure was repeated 2 times, one learning trial and one delayed recall trial (with a delay of 30 minutes). For the COWAT, participants were given one minute to name as many words as possible beginning with a given letter. The trial was repeated 3 times with 3

different letters (F, A, S) with combined scores used for analyses. The ANT is a measure of category verbal fluency in which participants were asked to name as many animals as he or she can within one minute. Two trials were conducted with the combined score used for analyses. Finally, the MAT involves a timed performance in which participants were asked to alternate between number and letter (i.e. 1-A, 2-B, 3-C…) as quickly as possible within 30 seconds.

Demographic, Health, and Lifestyle Data

Demographic data including age, sex, ethnicity, education, and income were collected at baseline during the in-home visit using the interviewer-administered questionnaire. Participant education level was determined by asking, "What is the highest degree, certificate or diploma you have obtained?". In order to assess household income, participants were asked, "What is your best estimate of the total household income received by all household members, from all sources, before taxes and deductions, in the past 12 months?".

Regarding health, hearing was assessed by asking participants, "Is your hearing, using a hearing aid if you use one, excellent, very good, fair or poor?". For use in our analyses, participant responses were dichotomized into two categories: good, very good, or excellent versus fair or poor. Participants were asked if they had ever received a physician diagnosis of diabetes, heart disease, or stroke.

Smoking status was classified as either current, never, or former based on participant responses to the interview questions "Have you smoked at least 100 cigarettes in your life?" and "At the present time, do you smoke cigarettes daily, occasionally (at least once in last 30 days), or not at all (not in last 30 days)?". A current smoker was defined as a person who reported smoking at least 100 cigarettes and currently smokes daily or occasionally while a former

smoker was someone who reported smoking at least 100 cigarettes in life but had not smoked in the last 30 days.

Statistical Analysis

Those with and without VI were compared for demographic, health, and lifestyle factors at baseline. Multiple linear regression was used to assess the association of vision-related variables at baseline with 3-year changes in cognitive scores adjusting for potential confounding variables including age, sex, ethnicity, household income, level of education, smoking status, diabetes, heart disease, stroke, province, and the relevant baseline cognitive variable (i.e. baseline COWAT for the COWAT change outcome). These variables were chosen based on previous research showing their importance to vision or cognitive impairment (3,6,25). Effect modification was tested by adding product terms into regression models. Statistical significance was considered to be $P < 0.05$. Sampling weights and strata variables were incorporated into all analyses using the SVY commands in STATA SE Version 16 (College Station, Texas).

RESULTS

Our analysis consisted of 27,412 individuals after excluding those missing vision data at baseline (n=431) and those lost to follow-up (n=2,254). Of the 2,254 who did not return to follow-up, 553 died (25%) and 938 withdrew (42%) with the remaining 763 (34%) either unable to be contacted or unable to complete data collection. Participants who were lost to follow-up were older, more likely to be female, had lower education, lower household income, were more likely to smoke, and were more likely to have diabetes, heart disease and stroke compared to those with who were not lost to follow-up.

Of our analytic sample, the mean age of participants, after correction for the complex survey design, was 59.5 years (SD=9.9) and 50.8% were female. Overall, at baseline, 5.7% of participants in the cohort had VI, 21.5% reported ever having had a cataract diagnosis, 3.2% reported a diagnosis of macular degeneration, and 3.9% reported a diagnosis of glaucoma.

Baseline characteristics of the cohort by VI status are presented in Table 1. Those with VI were more likely to be older, female, have lower education and annual household income levels, be current smokers, have diabetes, stroke and heart disease as compared to those without VI.

Visual Impairment and 3-year Change in Cognitive Scores

As shown in Table 2, persons with VI had smaller increases than those without VI over the 3-years of follow up on the RAVLT and RAVLT-Delayed scores (P<0.00). The increase for these two tests probably indicates a learning effect since the same list of words is used at baseline and follow-up. People with VI had a greater decline on the ANT than those without VI although this only reached borderline statistical significance (P=0.06). VI was not associated with changes in the COWAT or MAT scores.

VI and the 3-year change in cognitive scores modeled using linear regression is shown in Table 3. After adjusting for age, sex, ethnicity, education, income, smoking, diabetes, stroke, heart disease, baseline cognitive score, province and survey design, VI was associated with 3-year changes in RAVLT (β=-0.18, 95% confidence interval (CI)= -0.28, -0.07), RAVLT-Delayed (β=-0.13, 95% CI= -0.25, -0.02), and ANT (β=-0.95, 95% CI= -1.44, -0.45) scores while it was not associated with the COWAT or MAT.

Age-related Eye Disease and 3-year Change in Cognitive Scores

In Table 4, the results of the multiple linear regression models for glaucoma and 3-year changes in cognitive scores are shown. After adjusting for age, sex, ethnicity, education, income, smoking, diabetes, stroke, heart disease, baseline cognitive score, province and survey design, those with a report of glaucoma had a greater worsening in MAT change scores (β=-0.40, 95% CI -0.77, -0.04) than those who did not report glaucoma. There was a borderline association between glaucoma and the ANT (β=-0.55, 95% CI -1.11, 0.01, P=0.057). Glaucoma was not significantly associated with the other 3-year change in cognitive scores. AMD and cataract were not associated with any of the change in cognition scores (data not shown).

Effect Modification

No evidence of effect modification was found. None of the interaction terms between visual impairment/eye disease and hearing impairment, low education, or sex were statistically significant (P>0.05).

DISCUSSION

Using cognitive tests that did not rely on vision, we found that people with visual impairment performed worse on 3 out of 5 cognitive tests 3 years later than people without visual impairment. The 3 cognitive tests that were affected measured working memory and verbal fluency. Furthermore, people who reported having glaucoma performed worse on 1 out of the 5 cognitive tests: the Mental Alternation test, which measures executive functioning.

These relationships might be explained by the Common Cause hypothesis or the Disuse Hypothesis(7–10). Whatever ocular condition was causing the visual impairment may share a common pathology with cognitive disease. Sivak et al(7) described how diseases like age-

related macular degeneration (AMD) and glaucoma, which can affect visual acuity, and Alzheimer's disease share common characteristics like glial reactivity, neuroinflammation, and oxidative stress. Alternatively, the Disuse Hypothesis suggests that cognitive atrophy could develop due to difficulties doing activities that require vision(8–10). Research has shown that participating in more cognitive activities is associated with a reduced risk of developing dementia(26,27). Vision loss makes it difficult to do activities like reading, playing games, exercising, and socializing(28).

Of the limited number of longitudinal studies that have examined the possible associations of VI or age-related eye disease with subsequent cognitive decline, our results are in accordance with four studies(11–14) which found that VI was longitudinally associated with a decline in cognitive function. Zheng et al(11) reported statistically significant longitudinal associations between VI and cognitive function using cross-lagged models for a population-based sample (n=2,520) of older adults aged 65-84 years in Salisbury, Maryland (β = -0.074; SE, 0.015; P < .001). Lin et al(29) found that VI was associated with subsequent cognitive decline (OR= 1.78, 95% CI: 1.21-2.61) in community-residing older women (n=6,112) from four metropolitan areas of the United State (OR= 1.78, 95% CI: 1.21-2.61). Swenor et al(13) found using linear mixed effects models that visual acuity (HR=1.55; 95% CI 1.12-2.14), contrast sensitivity (HR=1.33; 95% CO 1.13-1.55) and stereo acuity (HR= 1.28 1.09-1.49) were longitudinally the associated with cognitive outcomes in a sample of community-dwelling, older adults (n= 3,075) aged 70-79 years, residing in Pittsburgh, Pennsylvania or Memphis, Tennessee. Lim et al(14) assessed the association between VI and decline in cognitive function over 6 years in a multi-ethnic Asian population (n=2,478) aged 60+ and found that VI at baseline

was associated with a decrease in cognitive scores (β = −0.27; 95% CI, −0.37 to −0.17; $P < .001$). Finally, Effendi-Tenang et al(15) found in a Malaysian sample of adults aged 55+ (n=1144) that VI was associated with a reduction on Montreal Cognitive Assessment (MoCA)-blind test scores after adjusting for age and gender ((β = 1.86; 95% CI, 1.08 to −3.21; $P = 0.025$).

Our results are in contrast to one study by Hong et al(16) who performed a prospective, population-based study of 3,654 participants of the Australian Blue Mountains Eye Study and reported that VI was not associated with cognitive decline over 5 years (OR 0.84; 95% CI 0.40-1.79) or 10 years (OR=1.09; 95% CI 0.52-2.30). Cognitive decline was measured using the MMSE-Blind test. The authors dichotomized the cognitive change scores such that they examined change >=3 MMSE-Blind points or not. Only 9 people had visual impairment and lost 3 or more MMSE-Blind points leading to very unstable estimates and a difficulty controlling for covariates.

The self-report of glaucoma was related to the MAT but not the other cognitive tests. To our knowledge, no other epidemiological studies have examined whether glaucoma is related to processing speed using a non-visual test. Previous studies have shown glaucoma to be related to worse scores on the verbal digit forward and backward tests and the logical memory test(30) , the MMSE-Blind(31) , and with increased Alzheimer's disease(32). Other studies have not shown associations with Alzheimer's disease(33,34).

A strength of this research was that this population-based, longitudinal dataset allowed us to measure the 3-year changes in cognitive test scores, to determine the temporality of the vision loss/eye disease and the onset of cognitive change, to adjust for a large number of potentially

confounding variables, and to examine potential effect modification. Further, multiple non-visual cognitive tests were used to assess cognitive change over time, thereby avoiding potentially spurious associations of vision and cognition measures or potential diagnostic misclassification common to registry data. A limitation of this study is the use of self-reported data on the presence of eye disease and chronic conditions. Furthermore, our results may not be generalizable to those excluded from the CLSA sampling frame which includes full-time members of the Canadian Armed Forces, those residing on a federal First Nations reserve or settlement, those living in a long-term care institution, those who are not a permanent resident or Canadian citizen, those not fluent in English or French, and those with cognitive impairment at baseline.

Associations between vision loss and cognitive function should be further explored longitudinally in an effort to identify potential pathways leading to increased risks of cognitive decline. Older adults should see their eye care providers regularly to reduce avoidable vision loss and should stay as cognitively active as possible.

DATA AVAILABILITY

This research has been conducted using the CLSA Comprehensive Dataset version 4.0 and Follow-up 1 Comprehensive Dataset version 1.0 under Application Number 190212. The CLSA is led by Drs. Parminder Raina, Christina Wolfson, and Susan Kirkland. The opinions expressed in this manuscript are the author's own and do not reflect the views of the Canadian Longitudinal Study on Aging.

DISCLOSURE OF INTEREST

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Table 1. Descriptive statistics of those with and without visual impairment

Variable	VI n= 1,925 Mean (SD)/Row %	No VI n=25,487 Mean (SD)/Row %
Age, Years	65.8 (12.1)	58.8 (9.4)
Sex		
Female (n=13,932)	5.7	94.3
Male (n= 13,480)	5.2	94.8
Ethnic or Racial Background		
White (n=25,897)	5.5	94.5
Black (n=220)	3.4	96.6
Asian (n=639)	6.0	94.0
Aboriginal (n=327)	6.4	93.6
Other (n=329)	5.3	94.8
Education		
More than Bachelor's (n=6,106)	4.9	95.1
Bachelor's (n=6,602)	4.6	95.4
Less than Bachelor's (n=14,660)	6.1	93.9
Annual Household Income		
≥ $150,000 (n=9,748)	3.7	96.4
$50,000 -$100,000 (n=9,162)	5.7	94.3
$20,000 - $50,000 (n=5,522)	8.1	91.9
<$20,000 (n=1,275)	10.3	89.7
Refused/ Don't know (n=1,705)	7.7	92.3
Smoking		
Current (n=2,315)	6.1	93.9
Former (n=11,906)	5.9	94.1
Never (n=13,190)	5.0	95.0
Diabetes		
None (n=22,646)	5.1	94.9
Type 1 (n=148)	8.5	91.5
Type 2 (n=2,400)	8.2	91.8
Suspect (n=1,928)	5.8	94.2
Stroke		
No (n=26,898)	5.4	94.7
Yes (n=423)	12.6	87.4
Heart Disease		
No (n=24,252)	5.1	94.9

Yes (n=3,020)	8.7	91.3

Table 2. Visual impairment and 3-year change in cognitive scores

Variable	VI n= 1,925 Mean (SD)	No VI n= 25,487 Mean (SD)	P value
Reyes	0.4 (2.1)	0.8 (1.9)	<0.00
Reyes Delayed	0.4 (2.3)	0.7 (2.1)	<0.00
COWAT (F, S, A)	0.4 (8.2)	0.8 (7.9)	0.17
ANT (Trials 1 & 2)	-0.9 (10.5)	-0.4 (9.7)	0.06
MAT	-0.6 (7.4)	-0.5 (6.4)	0.75

Table 3: VI and 3-year change in cognitive score using multiple linear regression*

Variable	Reyes β 95% CI	Reyes Delayed β 95% CI	COWAT β 95% CI	ANT β 95% CI	MAT β 95% CI
VI					
No	0.00	0.00	0.00	0.00	0.00
Yes	-0.18 (-0.28, -0.07)	-0.13 (-0.25, -0.02)	-0.28 (-0.72, 0.17)	-0.95 (-1.44, -0.45)	-0.16 (-0.50, 0.18)

*Adjusted for age, sex, ethnicity, education, income, smoking, diabetes, stroke, heart disease, baseline cognitive score, and province.

Table 4: Glaucoma and 3-year change in cognitive score using multiple linear regression*

Variable	Reyes β 95% CI	Reyes Delayed β 95% CI	COWAT β 95% CI	ANT β 95% CI	MAT β 95% CI
Glaucoma					
No	0.00	0.00	0.00	0.00	0.00
Yes	0.01 (-0.10, 0.13)	-0.10 (-0.22, 0.03)	0.24 (-0.26, 0.75)	-0.55 (-1.11, 0.01)	-0.40 (-0.77, -0.04)

*Adjusted for age, sex, ethnicity, education, income, smoking, diabetes, stroke, heart disease, baseline cognitive score, and province

CHAPTER 6: SUPPLEMENTARY ANALYSES

Effect Modification

In Tables 6-9, we present estimates of effect modification of the association between VI and eye disease with incident depressive symptoms at 3-years by poor hearing. Age, sex, annual household income, education, marital status, smoking status, comorbidity score, province and the complex survey design were also considered in the models. Based on separate models for each vision-related variable, we found no statistically significant effect modification by poor hearing.

Table 6. Interaction between hearing and visual impairment with incident depression during the 3-year follow up

Characteristic	**Adjusted RR***	**P value**
Visual impairment	0.96	0.71
Poor hearing	1.27	0.00
Visual impairment x poor hearing	1.17	0.55

*****Adjusted for age, sex, annual household income, education, marital status, smoking status, comorbidity score, province and the complex survey design

Table 7. Interaction between hearing and AMD with incident depression during the 3-year follow up

Characteristic	**Adjusted RR***	**P value**
AMD	1.22	0.11
Poor hearing	1.28	0.00
AMD x poor hearing	1.40	0.25

*****Adjusted for age, sex, annual household income, education, marital status, smoking status, comorbidity score, province and the complex survey design

Table 8. Interaction between hearing and glaucoma with incident depression during the 3-year follow up

Characteristic	Adjusted RR*	P value
Glaucoma	1.19	0.13
Poor hearing	1.31	0.00
Glaucoma x poor hearing	0.79	0.41

*****Adjusted for age, sex, annual household income, education, marital status, smoking status, comorbidity score, province and the complex survey design

Table 9. Interaction between hearing and cataract with incident depression during the 3-year follow up

Characteristic	Adjusted RR*	P value
Cataract	1.24	0.00
Poor hearing	1.21	0.07
Cataract x poor hearing	1.17	0.30

*****Adjusted for age, sex, annual household income, education, marital status, smoking status, comorbidity score, province and the complex survey design

In Tables 10-13, we present estimates of effect modification of the association between VI and eye disease with incident depressive symptoms at 3-years by female sex. Age, annual household income, education, marital status, smoking status, comorbidity score, province and the complex survey design were also considered in the models. Based on separate models for each vision-related variable, we found no statistically significant effect modification by female sex.

Table 10. Interaction between female sex and visual impairment with incident depression during the 3-year follow up

Characteristic	Adjusted RR*	P value
Visual impairment	0.96	0.84
Female sex	1.51	0.00
Visual impairment x female sex	1.03	0.89

*****Adjusted for age, annual household income, education, marital status, smoking status, comorbidity score, province and the complex survey design

Table 11. Interaction between female sex and AMD with incident depression during the 3-year follow up

Characteristic	**Adjusted RR***	**P value**
AMD	1.33	0.15
Female sex	1.51	0.00
AMD x female sex	0.97	0.89

*****Adjusted for age, annual household income, education, marital status, smoking status, comorbidity score, province and the complex survey design

Table 12. Interaction between female sex and glaucoma with incident depression during the 3-year follow up

Characteristic	**Adjusted RR***	**P value**
Glaucoma	1.03	0.88
Female sex	1.50	0.00
Glaucoma x female sex	1.19	0.43

*****Adjusted for age, annual household income, education, marital status, smoking status, comorbidity score, province and the complex survey design

Table 13. Interaction between female sex and cataract with incident depression during the 3-year follow up

Characteristic	**Adjusted RR***	**P value**
Cataract	1.35	0.00
Female sex	1.52	0.00
Cataract x female sex	0.91	0.38

*****Adjusted for age, annual household income, education, marital status, smoking status, comorbidity score, province and the complex survey design

In Tables 14-17, we present estimates of effect modification of the association between VI and eye disease with incident depressive symptoms at 3-years by education level (less than a Bachelor's degree). Age, sex, annual household income, marital status, smoking status, comorbidity score, province and the complex survey design were also

considered in the models. Based on separate models for each vision-related variable, we found no statistically significant effect modification by having an education less than a Bachelor's degree.

Table 14. Interaction between education level and visual impairment with incident depression during the 3-year follow up

Characteristic	**Adjusted RR***	**P value**
Visual impairment	0.74	0.24
Less than a Bachelor's degree	1.19	0.03
Visual impairment x less than a Bachelor's degree	1.46	0.19

*****Adjusted for age, sex, annual household income, marital status, smoking status, comorbidity score, province and the complex survey design

Table 15. Interaction between education level and AMD with incident depression during the 3-year follow up

Characteristic	**Adjusted RR***	**P value**
AMD	1.54	0.13
Less than a Bachelor's degree	1.22	0.01
AMD x less than a Bachelor's degree	0.93	0.81

*****Adjusted for age, sex, annual household income, marital status, smoking status, comorbidity score, province and the complex survey design

Table 16. Interaction between education level and glaucoma with incident depression during the 3-year follow up

Characteristic	**Adjusted RR***	**P value**
Glaucoma	1.49	0.09
Less than a Bachelor's degree	1.25	0.00
Glaucoma x less than a Bachelor's degree	0.66	0.12

*****Adjusted for age, sex, annual household income, marital status, smoking status, comorbidity score, province and the complex survey design

Table 17. Interaction between education level and cataract with incident depression during the 3-year follow up

Characteristic	**Adjusted RR***	**P value**
Cataract	1.41	0.00
Less than a Bachelor's degree	1.26	0.01
Cataract x less than a Bachelor's degree	0.85	0.26

*****Adjusted for age, sex, annual household income, marital status, smoking status, comorbidity score, province and the complex survey design

In Tables 18-19, we present estimates of effect modification of the association between VI and glaucoma with 3-year changes in cognitive score by poor hearing. Age, sex, ethnicity, annual household income, smoking status, stroke, heart disease, baseline cognitive score, province and the complex survey design were also considered in the models. We found no statistically significant effect modification.

Table 18: Interaction between hearing and VI with 3-year change in cognitive score using multiple linear regression*

Variable	Reyes β 95% CI	Reyes Delayed β 95% CI	ANT β 95% CI	MAT β 95% CI
VI	-0.20 (-0.32, -0.09)	-0.16 (-0.28, -0.04)	-0.97 (-1.51, -0.43)	-0.21 (-0.58, 0.15)
Poor hearing	-0.13 (-0.22, -0.04)	-0.13 (-0.22, -0.03)	0.07 (-0.37, 0.50)	-0.34 (-0.63, -0.04)
VI x poor hearing	0.23 (-0.05, 0.50)	0.24 (-0.08, 0.56)	0.15 (-1.18, 1.48)	0.45 (-0.49, 1.40)

*Adjusted for age, sex, ethnicity, education, income, smoking, diabetes, stroke, heart disease, baseline cognitive score, and province.

Table 19: Interaction between hearing and Glaucoma with 3-year change in cognitive score using multiple linear regression*

Variable	Reyes β 95% CI	Reyes Delayed β 95% CI	ANT β 95% CI	MAT β 95% CI
Glaucoma	0.03 (-0.09, 0.15)	-0.07 (-0.20, -0.06)	-0.39 (-1.00, 0.22)	-0.32 (-0.71, 0.07)
Poor hearing	-0.11 (-0.19, -0.02)	-0.10 (-0.19, -0.00)	0.17 (-0.26, 0.60)	-0.28 (-0.56, 0.01)
Glaucoma x poor hearing	-0.18 (-0.54, 0.17)	-0.21 (-0.55, 0.13)	-1.40 (-2.93, 0.14)	-0.78 (-1.88, 0.32)

*Adjusted for age, sex, ethnicity, education, income, smoking, diabetes, stroke, heart disease, baseline cognitive score, and province.

In Tables 20-21, we present estimates of effect modification of the association between VI and glaucoma with 3-year changes in cognitive score by female sex. After adjusting for age, ethnicity, annual household income, smoking status, stroke, heart disease, baseline cognitive score, province and the complex survey design, we found no statistically significant effect modification.

Table 20: Interaction between female sex and VI with 3-year change in cognitive score using multiple linear regression*

Variable	Reyes β 95% CI	Reyes Delayed β 95% CI	ANT β 95% CI	MAT β 95% CI
VI	-0.11 (-0.24, 0.02)	-0.04 (-0.18, 0.10)	-0.97 (-1.64, -0.29)	0.11 (-0.40, 0.61)
Female sex	0.66 (0.61, 0.72)	0.71 (0.65, 0.77)	-0.15 (-0.41, 0.11)	-0.50 (-0.68, -0.33)
VI x female sex	-0.13 (-0.33, 0.08)	-0.19 (-0.40 0.03)	0.04 (-0.93, 1.01)	-0.51 (-1.17, 0.16)

*Adjusted for age, ethnicity, education, income, smoking, diabetes, stroke, heart disease, baseline cognitive score, and province.

Table 21: Interaction between female sex and Glaucoma with 3-year change in cognitive score using multiple linear regression*

Variable	Reyes β 95% CI	Reyes Delayed β 95% CI	ANT β 95% CI	MAT β 95% CI
Glaucoma	-0.03 (-0.18, 0.12)	-0.01 (-0.18, 0.16)	-0.40 (-1.24, 0.44)	-0.59 (-1.15, -0.04)
Female sex	0.65 (0.60, 0.71)	0.71 (0.65, 0.77)	-0.13 (-0.40, 0.13)	-0.54 (-0.71, -0.37)
Glaucoma x female sex	0.07 (-0.15, 0.30)	-0.17 (-0.41, 0.07)	-0.30 (-1.41, 0.81)	0.37 (-0.36, 1.09)

*Adjusted for age, ethnicity, education, income, smoking, diabetes, stroke, heart disease, baseline cognitive score, and province.

In Tables 22-23, we present estimates of effect modification of the association between VI and glaucoma with 3-year changes in cognitive score by education level (less than a Bachelor's degree). After adjusting for age, ethnicity, annual household income, smoking status, stroke, heart disease, baseline cognitive score, province and the complex survey design, we found no statistically significant effect modification by having an education less than a Bachelor's degree.

Table 22: Interaction between education level and VI with 3-year change in cognitive score using multiple linear regression*

Variable	Reyes β 95% CI	Reyes Delayed β 95% CI	ANT β 95% CI	MAT β 95% CI
VI	-0.32 (-0.57, -0.06)	-0.22 (-0.47, 0.03)	-1.19 (-2.28, -0.10)	-0.47 (-1.21, 0.27)
Less than a Bachelor's degree	-0.43 (-0.50, -0.36)	-0.53 (-0.61, -0.45)	-1.43 (-1.79, -1.08)	-0.89 (-1.12, -0.66)
VI x less than a Bachelor's degree	0.17 (-0.12, 0.45)	0.13 (-0.16 0.41)	0.26 (-0.98, 1.51)	0.49 (-0.37, 1.34)

*Adjusted for age, sex, ethnicity, income, smoking, diabetes, stroke, heart disease, baseline cognitive score, and province.

Table 23: Interaction between education level and Glaucoma with 3-year change in cognitive score using multiple linear regression*

Variable	Reyes β 95% CI	Reyes Delayed β 95% CI	ANT β 95% CI	MAT β 95% CI
Glaucoma	-0.13 (-0.38, 0.13)	-0.20 (-0.49, 0.09)	-0.32 (-1.43, 0.78)	0.04 (-0.76, 0.84)
Less than a Bachelor's degree	-0.43 (-0.50, -0.36)	-0.53 (-0.60, -0.45)	-1.41 (-1.76, -1.06)	-0.84 (-1.07, -0.61)
Glaucoma x less than a Bachelor's degree	0.18 (-0.11, 0.48)	-0.17 (-0.41, 0.07)	-0.39 (-1.71, 0.93)	-0.71 (-1.63, 0.22)

*Adjusted for age, sex, ethnicity, income, smoking, diabetes, stroke, heart disease, baseline cognitive score, and province.

CHAPTER 7: DISCUSSION

Summary of Overall Findings

This thesis examined two potential consequences of visual impairment and eye disease: depression and cognitive decline. VI, AMD, and glaucoma were not associated with incident depression although cataract was (relative risk=1.20, 95% confidence interval 1.05, 1.37). VI was associated with 3-year changes on 3 out of 5 cognitive tests including the RAVLT (β=-0.18, 95% CI= -0.28, -0.07), RAVLT-Delayed (β=-0.13, 95% CI= -0.25, -0.02), and ANT (β=-0.95, 95% CI= -1.44, -0.45). Glaucoma was associated with greater declines on the MAT (β=-0.40, 95% CI= -0.77, -0.04) while it was not associated with any other cognitive change outcomes. AMD and cataract were not associated with any cognitive change outcomes.

The effect sizes were relatively small. For example, a report of cataract was associated with a 20% higher risk of the development of depression. A person with VI performed almost 1 point worse on the ANT 3-years after baseline than someone without VI. This means that they reported almost 1 fewer animal names in 1 minute than someone without VI. Whether these findings are clinically meaningful or not is difficult to say. With only two wavesof data, it is not clear whether this decline will be a linear decline or whether it might become steeper with time.

No effect modification was detected between hearing loss, lower education, or sex with any of the VI or eye disease measures for either cognitive decline or depression.

Depression Findings

Our data indicated that the risk of depression is 20% higher in individuals who reported ever having received a physician diagnosis of cataract. Individuals with VI, AMD and glaucoma were not found to have increased risks of developing such depressive symptoms at 3-years of follow-up. A potential explanation for our findings is that cataract is often very disruptive to visual function due to effects on visual acuity, the ability to see contrast, and sensitivity to glare. It can cause problems with driving, especially at night. It cannot be treated with medication like glaucoma, requires having surgery done, and even after surgery, vision can be destabilized for a period of time until both eyes have been operated upon. Complications can sometimes result from the surgery requiring additional surgery. By contrast, glaucoma can often be treated by medications. AMD, while difficult to manage in its later stages, only requires monitoring at earlier stages. Perhaps a larger association with AMD would have been found if information on disease severity was available.

Cognitive Findings

VI was associated with the cognitive tests that measure working memory and verbal semantic fluency. VI was not associated with verbal phonetic fluency or processing speed. Working memory involves the storage and manipulation of information over a short period. One could speculate that working memory could suffer if a person lost visual function and had a dramatic reduction in activities that requires the use of working memory (e.g. grocery shopping, cooking, driving, playing board

games). If working memory is like a muscle and it works better when used, disuse could lead to worse performance. Indeed, researchers have found that training interventions can improve working memory[164]. Verbal semantic fluency involves naming as many items of a specific category in a short period of time. It requires verbal ability, to find the words, and executive control to focus on the task and avoid repetition. People with vision loss may have difficulties with both reading and social interaction, leading to less time spent doing these activities, which may affect their ability to retrieve words. Indeed, some studies do indicate a relationship between social relationship and verbal fluency[165].

Strengths of the Research

The longitudinal design of the CLSA allowed us to measure health trajectories over 3-years using a large population-based sample of older adults. A further strength of this dataset was that we were able to adjust for a large number variables known to be associated with VI, eye disease, depression and cognition, and to examine potential effect modification thereby furthering knowledge of the complex interplay of risk factors. We appropriately modeled the non-linear relationship between age and incident depression and utilized multiple non-visual cognitive tests to assess cognitive change scores over time, thereby avoiding potentially spurious associations of vision and cognition measures or potential diagnostic misclassification common to registry data.

Generalizability of Research Findings

The CLSA study excluded those who could not speak English or French, those living on a First Nations reserve or in an institution, those in the military and those with overt cognitive impairment. Further, the individuals recruited via random digit dialing were required to have a landline telephone. Therefore, generalizability of our results to more remote areas in Canada and from areas outside of the 11 data collection site locations as well as to groups other than those studied remains unknown. For example, it is possible that having vision loss in an institution may be more strongly associated with the risk of depression or cognitive decline than having vision loss in a community-dwelling environment. Additional research on the risk of vision loss in institutions or the Far North is warranted.

Risk of Bias

Some people were missing data on baseline visual acuity (n=431). These individuals were found to be an average of two years older, which may indicate an underestimation of the number of VI cases at baseline in our study, as VI is strongly associated with age. Further, individuals with missing depression data at baseline or follow up were also excluded (n=893). These individuals were, on average, older, more likely to be female and had lower education levels and total household incomes than those with complete depression data indicating that our estimate of the incidence of depression may be underestimated as these factors have all been confirmed to be significantly related to increased risk of MDD[51,54]. However, the percentage of those

with missing data was low (3.8%) so it is unlikely to have substantially affected our results.

The main risk of bias of the present analysis is the use of self-reported data including the data on eye disease, demographic, lifestyle and health-related factors. There was no ophthalmological exam confirming reports of eye disease. For example, past studies have found that most major eye diseases are likely underestimated via the methods of self-reporting[166]. The use of self-reported eye disease is prone to misclassification due to a lack of patient recall, awareness and understanding of diagnoses[166]. However, some diseases may be more prone to misclassification than others. For example, glaucoma may be more prone to misclassification as many people with glaucoma do not know they have it until rather late in the disease process. Furthermore, patients may be confused by other conditions like ocular hypertension that require treatment similar to glaucoma leading to an over-estimation of the diagnoses. *Linton et al*[166] assessed the validity of self-reported cataract and AMD using data from the population-based Beaver Dam Eye Study. Their findings indicate that a self-reporting of cataract and AMD both had a low sensitivity and a high specificity, and that the sensitivity was much lower for AMD than for cataract[166]. *Patty et al*[167] reported similar findings using data from the Los Angeles Latino Eye Study. They found self-reporting of cataract, AMD, and glaucoma all had a low sensitivity and high specificity and that the accuracy of self-report decreased with increasing time since last eye examination[167]. Further, they confirmed self-reporting of AMD as having a lower sensitivity than cataract and glaucoma and that inaccurate self-report was

independently associated with better visual acuity, having less comorbidity, and a lower level of education[167]. In light of this, our findings with eye disease should be confirmed in studies that have diagnosed eye disease.

Another limitation of our study is that the majority of people with cataract did not know if they had had cataract surgery or not. Therefore, we were unable to determine if the increased risk of depression was in those who had had surgery, in those who had not had surgery, or in both.

Next, social-desirability bias may have led participants to under-report their chronic conditions or the frequency at which they engage in unhealthy behaviours such as smoking. However, CLSA interviewers were trained to ask questions in a non-judgmental and standardized way.

Finally, due to space constraints, the test distance of the ETDRS chart utilized in the CLSA data collection sites was 2 meters rather than the current gold standard of 4 meters. This may have led to a slight overestimation of VI at baseline as visual acuity scores have been found to be systematically lower when measured at shorter test distances[168].

Future Research

Future research should assess if the increased risk of depression is isolated to those with current cataract who are awaiting surgery or if it is also present in those who have already had cataract surgery. Additional research should also be done on people with clinically diagnosed eye disease and their cognitive changes over time. Research on the mechanisms underlying these pathways is also needed. As participation in lifestyle activities may differ greatly in those with vision loss, potential mediation pathways should be explored, especially once the third round of CLSA data become available.

Implications of Study Findings

Additional research is needed before interventions are developed and implemented into care. However, if our research is confirmed and greater knowledge is gained about underlying mechanisms, interventions could be developed and targeted towards the affected groups. For example, a depression screening could be given by nurses within the ophthalmology clinics with those screening positive given information about how to access treatment. Patients with depression could also be referred to self-care management programs if they are not interested in antidepressants or psychotherapy[169]. Likewise, cognitive training exercises that are appropriate for people with vision loss could be developed and tested.

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