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Age-Related Eye Disease and Cognitive Function

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Résumé

Objectif: Évaluer la relation entre la fonction cognitive chez les personnes âgées atteintes de dégénérescence maculaire reliée à l'âge (DMLA), de glaucome ou de dystrophie cornéenne de Fuchs et les comparer avec les personnes âgées n'ayant pas de maladie oculaire.

Devis: Étude transversale de population hospitalière.

Participants: 420 participants (113 avec la DMLA, 66 avec la dystrophie cornéenne de Fuchs, 130 avec le glaucome et 111 témoins).

Méthodes: Nous avons recruté les patients à partir de la clinique d'ophtalmologie de l'Hôpital Maisonneuve-Rosemont (Montréal, Canada) de septembre 2009 à septembre 2013. Les patients atteints de la DMLA ou de la maladie de Fuchs ont une acuité visuelle inférieure à 20/40 dans les deux yeux, tandis que les patients avec du glaucome ont un champ visuel dans le pire œil inférieur ou égal à -4dB. Les patients contrôles, qui ont été recrutés à partir des mêmes cliniques, ont une acuité visuelle et un champ visuel normaux. Nous avons colligé des données concernant la fonction cognitive à partir du test Mini-Mental State Exam (MMSE)-version aveugle. Pour mesurer la fonction visuelle, nous avons mesuré l'acuité visuelle, la sensibilité au contraste et le champ visuel. Nous avons également révisé le dossier médical. Pour les analyses statistiques nous avons utilisé la régression linéaire.

Critère de jugement principal: MMSE-version aveugle.

Résultats: Les trois maladies oculaires ont été associées à une limitation de la cognition. Le score de MMSE-version aveugle se situe de 0.7 à 0.8 unités plus basses par rapport au groupe contrôle. Comparativement aux contrôles, les patients avec maladies oculaires ont eu un score moyen diminué ($P < 0.05$). Le niveau d'éducation élevé est associé à une meilleure cognition ($P < 0.001$).

Conclusions: Nos résultats suggèrent que les maladies oculaires sont associées à une diminution de la fonction cognitive chez les personnes âgées. De futures études sont nécessaires pour évaluer l'impact des maladies oculaires sur le déclin cognitif chez cette population pour pouvoir envisager des interventions ciblées qui pourraient les aider à maintenir leur indépendance le plus longtemps possible.

Mots-clés : cognition, maladie oculaire, vieillissement

Abstract

Objective: To examine the extent of cognitive impairment in patients with age-related macular degeneration (AMD), glaucoma, or Fuchs corneal dystrophy as compared to a control group of older adults with good vision.

Design: Cross-sectional hospital-based study.

Participants: 420 people (113 with AMD, 66 with Fuchs, 130 with glaucoma, and 111 controls).

Methods: Patients were recruited from the ophthalmology clinic of Maisonneuve-Rosemont Hospital (Montreal, Canada) from September 2009 until September 2013. Patients with AMD and Fuchs had to have visual acuity in the better eye of worse than 20/40 while patients with glaucoma had to have visual field deficit in their worse eye of at least -4dB. Control patients who had normal visual acuity and visual field were recruited from the same clinic. Cognitive status was measured using the Mini-Mental State Exam (MMSE) Blind Version. Visual acuity, contrast sensitivity, and visual field were assessed, and the medical record was reviewed. Linear regression was used.

Main Outcome Measures: Mini-Mental State Exam (MMSE) Blind Version

Results: The three eye diseases were associated with of cognitive impairment. Compared to controls, patients with age-related eye disease had lower MMSE Blind scores ($p < 0.05$). Scores were between 0.7-0.8 units lower than the control group. Better education was associated with better cognition ($p < 0.001$).

Conclusions: Our results suggest that eye diseases are associated with cognitive impairment. It is important to further explore the impact of eye disease on cognitive function in this

population in order to develop interventions that would help affected older adults maintain their independence.

Keywords : cognition, eye disease, aging

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LIST OF ABBREVIATIONS

AAMI	Age-Associated memory impairment
AChEIs	ACethycholinesterases inhibitors
AD	Alzheimer disease
ADAS-cog	Alzheimer Disease Assessment Scale-Cognitive Subscale
ADL	Activities of Daily Living
aMCI	amnestic MCI
AMD	Age-Related Macular Degeneration
AMT	Abbreviated Mental Test
ANOVA	Analysis of variance
APOE	Apolipoprotein
AREDS	Age-Related Eye Disease Study
β	Linear Regression Coefficient
CAMDEX	Cambridge Mental Disorder OF Eldery
CI	Confidence interval
CIND	Cognitive impairment with no dementia
CLA	Cognitive leisure activities
CSHA	Canadian Study of Health and Aging
dB	Decibel
DSEK	Descemet stripping endothelial keratoplasty
DSST	Digit Symbol Substitution Test
ε4	Epsilon 4
ETDRS	Early Treatment of Diabetic Retinopathy Study
FCD	Fuchs' Corneal Dystrophy
FDT	Frequency Doubling Technology
GPCOG	General Practitioner Assessment of Cognition
HMR	Hôpital Maisonneuve-Rosemont

IADL	Instrument activity of daily living
ILSE	Interdisciplinary Longitudinal Study on Adult Development and Aging
IOP	Intra-ocular pressure
LALES	Los Angeles Latino Eye Study
log	Logarithm
logMAR	Logarithm of Minimal Angle of Resolution
Max	Maximum
MCI	Mild cognitive impairment
MD	Mean Deviation
MESA	Multi-Ethnic Study of Atherosclerosis
MIS	Memory Impairment Screen
MMSE	Mini-Mental State Exam
MMSE-blind	Blind Version of the MMSE
MOCA	Montreal Cognitive Assessment
3MSE	Modified Mini-Mental State Examination
n	Number of subjects
NFL	Nerve Fiber Layer
OR	Odd Ratio
P	P value
PACG	Primary angle closure glaucoma
PAR	Population attributable risk
POAG	Primary Open Angle Glaucoma
RCT	Randomized Clinical Trial
RGC	Retinal ganglion cell
RPE	Retinal pigment epithelium
SPMSQ	Short Portable Mental Status Questionnaire
SD	Standard Deviation

UV	Ultra-Violet
WMS–R	Wechsler Memory Scale–Revised

Dedication

I wish to express my deepest thanks and gratitude to my supervisor Dr Ellen Freeman, who provided me with tight guidance and advice. I owe her a lot for the tremendous source of knowledge she has been to me. It was a real pleasure working with her.

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CHAPTER I: INTRODUCTION

I.1. Cognitive impairment in older adults

Cognitive impairment is an acquired deficit in memory, problem solving, orientation, or abstraction[1]. The risk of cognitive impairment increases with older age. Other established risk factors for cognitive impairment identified in longitudinal studies include current smoking, diabetes, apolipoprotein E ε4 allele, depressive symptoms, and metabolic syndrome[2]. There is some evidence to suggest that eye disease or visual impairment may be risk factors for cognitive impairment although there is no consensus and the existing research has methodological limitations (discussed in Section II.2). There is a need for more research to determine the role of vision loss on cognitive function.

I.2. Specific objectives and hypotheses

The goal of this research was to determine if people with eye disease have worse cognition than people with normal vision. We focused on eye diseases that are age-related and that affect different components of visual function such as age-related macular degeneration, glaucoma, and Fuchs corneal dystrophy. We hypothesized that people with central vision loss would have the worst cognition, followed by people with peripheral vision loss, followed by people with normal vision.

I.3. Significance of this research

This research is important for many reasons. If vision loss causes cognitive impairment, then intervention efforts need to be targeted towards people with vision loss. As the Canadian population ages, more and more people are going to be afflicted with age-related eye disease and therefore may be at risk for cognitive impairment.

I.4. Organization of the thesis

This thesis is composed of 5 chapters: an introduction, a literature review, sample size calculation, an article that has been submitted for publication, and a discussion section.

CHAPTER II: LITERATURE REVIEW

II.1. Definition of cognitive impairment

As mentioned above, cognitive impairment is an acquired deficit in memory, problem solving, orientation, or abstraction. Cognitive impairment may be caused by normal aging-related changes or age-related diseases. There are differing severities of cognitive impairment that are still in the process of being defined with broad agreement. Mild cognitive impairment (MCI) and cognitive impairment with no dementia (CIND) are evolving terms that involve greater than expected cognitive decline for a person's age and educational level and no more than mild functional impairment that does not yet meet the definition of dementia[2]. Dementia is impaired cognition that results in functional impairment. The major cause of dementia is Alzheimer's disease accounting for about 60% of all cases. Other causes of dementia include stroke, brain injury, tumor, alcohol abuse, infection, and others.

People with MCI are at a higher risk of developing dementia[3]. There are controversies about the definition of MCI. A multidisciplinary and a worldwide group of experts from Asia, Australia, Europe and North America proposed MCI general criteria such that it (i) refers to non-demented persons with cognitive deficits measurable in some form or another, and (ii) represents a clinical syndrome that can be utilized to classify persons who do not fulfil a diagnosis of dementia, but who have a high risk of progressing to a dementia disorder[4].

Many different terms have been used by studies reporting MCI, e.g. cognitive impairment with no dementia (CIND), age-associated memory impairment (AAMI), MCI, and amnestic MCI (aMCI). This has caused confusion in the literature.

II.2. Measurement of cognitive impairment in research

There are many different diagnostic tools that have been described in the literature. There is no single cognitive assessment tool that is considered to be the gold standard. Many studies have examined tools to give a brief cognitive assessment during primary care visits.

A systematic review for the U.S. Preventive Services Task Force, included 55 fair- to good-quality diagnostic accuracy studies of brief screening instruments that could be delivered by a clinician in primary care in 10 minutes or less or self-administered in 20 minutes or less[5]. The studies varied in mean age (range 69 to 95 years) and prevalence of dementia (range from 1.2% to 47.1%). Lin et al found that the most commonly used measures were the Mini-Mental State Exam (MMSE) and the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-cog)[5].

The MMSE is the most widely used. It can be administered in 5-10 minutes and consists of a variety of questions[6]. The questions have been grouped into seven categories, each representing a different cognitive domain: Orientation to time (five points), orientation to place (five points), registration of three words (three points), attention and calculation (five points),

recall of three words (three points), language (eight points) and visual construction (one point). The most common cut-off points to detect dementia are 23/24 and 24/25. The scores range from 0 to 30. The lower the score, the cognitive impairment is important.

The Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-cog) is composed of 13 items[7]. The ADAS-cog identifies many domains: Memory word recall, following commands, constructional praxis, naming objects, ideational praxis, orientation, word recognition, recall of test instructions, spoken language ability and language, word-finding difficulty, comprehension, executive function and number cancellation. The total score on the ADAS-cog range from 0 to 70, with a higher score indicating greater cognitive impairment[7].

We used the the Blind Version of the MMSE (MMSE-blind) in our study, employed by Reischies and Geiselmann[8], from which eight items involving image processing in the test situation (two items with naming, reading, and obeying a sentence, writing a sentence, copying, and three items for performing a three-stage command) had been deleted. The MMSE-blind can be used to assess orientation to time and place, memory, attention, calculation, and language. These areas of cognitive functioning have been found to have discriminative power in the detection of dementia. The number of items of the full MMSE was reduced by 27%, leaving a total possible score of 22 for the MMSE-blind.

Busse et al examined the validity of the MMSE-blind and found that a cut-off point of 16 had 99% sensitivity and 94% specificity. The Test–retest reliability for the MMSE-blind was assessed in a sample of 35 subjects aged 75 years and older[9]. It was carried out within a 2-weeks interval. Busse et al obtained a significant K value of 0.5. Increased scores on retest were found indicating practice effects (Wilcoxon-test, $z = 2.43$, P =0.015)[9].

The Alzheimer's Association convened a group of experts to identify brief cognitive assessments most suitable or most used for the detection of cognitive impairment during the Medicare Annual Wellness in primary care settings. The experts focused on systematic evidence review studies published since 2000. They found that Memory Impairment Screen (MIS)[10], the General Practitioner Assessment of Cognition (GPCOG) and the Mini-Cog[11] as most suited for routine use in primary care[12-17].

Other tests that are used in research include the Montreal Cognitive Assessment (MOCA)[18] and the Digit Symbol Substitution Test (DSST)[19,20]. The version of the MoCA is a one-page 30-point test administered in 10 minutes. Details on the specific MoCA items are as follows. The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately 5 minutes. Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point). Multiple aspects of executive functions are assessed using an alternation task adapted from the Trail Making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points). Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and

digits forward and backward (1 point each). Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task. Finally, orientation to time and place is evaluated (6 points). The Digit Symbol Substitution Test (DSST), a subtest of the Wechsler Adult Intelligence Scales is a measure of psychomotor performance scored as the translation of numbers (1–9) corresponding to novel symbols in 90 seconds, with a maximum score of 93[19,20].

A summary of these cognitive tests as well as others are mentioned in Table IV.

II.3. Frequency of cognitive impairment

The frequency of CIND and dementia and the measurement tools found in population-based studies throughout the world are shown in Table V.

Based on the United Nations predictions for dementia, the number of demented people in the world will increase from 25.5 million in 2000 to 63 million in 2030 and to 114 million in 2050.

In Canada, there are 60 150 new cases of dementia each year and there are currently about 450 000 people with all forms of dementia[24]. The Canadian Study of Health and Aging (CSHA), a large population study of cognition (n= 10,263), has estimated the prevalence of dementia[25] and CIND[3] to be 8 and 16.8% in the population over age 65, respectively. The most common types of dementia are Alzheimer disease and vascular dementia.

The Italian Longitudinal Study of Aging reported a prevalence of dementia and CIND of 10.7 and 5.5 % respectively in subjects between 65 and 84 years old [26]. In the Kungsholmen project done in 2368 older adults in Stockholm, Sweden, the authors found 14.7% of subjects over 75 years old with CIND (n=1,435)[27] and 5 % with dementia (n=1,810)[28].

In the Taiwanese nationwide population-based cross-sectional survey (n=10,432), 18.76 % adults aged over 65 years had CIND and 8.04 % had dementia[29]. The prevalence of cognitive impairment ranged from 22.4% for participants in the Cardiovascular Health Study[30](n=5,201, aged 65 and older) to 21% in the Established Populations for Epidemiologic Studies of the Elderly in the United States, with participants aged 71 years and older and cognitive function assessed by the Short Portable Mental Status Questionnaire (SPMSQ).

Reported rates of CIND ranged widely mainly because of use of different measurement tools and cut-offs, different age groups, and different inclusion criteria.

II.4. Economic consequences of severe cognitive impairment

Canadian researchers have estimated the cost of caring for patients with severe cognitive impairment. Alzheimer disease is not only devastating to both patients and affected families but also is a considerable financial burden on society, particularly as the disease progresses. In Canada, it is estimated that the annual economic burden is $10 000 for each person with mild Alzheimer disease and $37 000 for severe Alzheimer disease[31]. For every person with dementia who does not live in a long term care facility, there is also the burden to the caregiver, which

usually falls on the patient's spouse or child[31]. Caregivers often suffer significant health problems themselves due to the stress of taking care of a person with dementia[31].

II.5. Disability consequences of cognitive impairment

Cognitive impairment can lead to disability and premature mortality. The 10-year trajectories of incident disability in the Iowa Established Populations for Epidemiological Studies of the Elderly cohort which included 3,673 participants aged 65 and older found that in people with MCI without instrument activity of daily living (IADL) limitations. IADL disability is defined as difficulty or dependence with any of three instrumental activities (shopping, preparing meals, or doing housework).the probability of ADL disability was the same as in the cognitively normal group. However, individuals with MCI plus prevalent IADL disabilities were much more likely to develop ADL disability, a prerequisite for a diagnosis of dementia[32].

A UK study of older people aged 75 years and over, showed that increased cognitive impairment at baseline was associated with an increased 5-year risk of physical disability on five activities of daily living (ADL)[33].

In the Manitoba Longitudinal Study on Ageing, good mental status measures at baseline were associated with a higher odds of successful aging including functioning well at home over a 12-year period, in 3,573 representative sample of elderly individuals aged 65-84 years[34]. In the PAQUID study, a study over one year follow-up consisted in 1850 subjects aged 65 and over, absence of cognitive impairment assessed by MMS at baseline was associated with

recovery to independence on activities of daily living and mobility in subjects initially dependent[35].

In the Canadian Study of Health and Aging (CSHA) data from 9,008 community-dwelling individuals aged 85 years and older, Griffith et al found higher population attributable risk (PARs) for cognitive impairment in the older age groups and for men for disability in terms of ADL and IADL[72].

In a Dutch study[36], cognitive impairment (MMSE ≤18) was found to account for 24% of walking disability in the oldest group of elderly. Two studies from Hong Kong[37] and Sweden[38] indicated that dementia had a PAR of 23.2 and 49.2% for functional disability in the elderly based on ADL. Dodge et al. also reported PARs ranging from 18.7 to 36.3% for different components of ADL among community-dwelling Japanese elders[39].

Survival rates for MCI patients, aged 85 years and older, over a 7-year period were midway between those for normal elderly people and Alzheimer's disease patients, with a cumulative mortality risk twice that of the general population[40]. Obviously, cognitive impairment is a major cause of disability and premature mortality.

II.6. Prevention

Fortunately, there are some ways to prevent cognitive impairment. The identification of people at potential risk of dementia to begin early therapeutic intervention is important, because it may

lessen distress for both patient and family, minimise the risk of accidents, prolong autonomy, and perhaps even ultimately prevent the onset of the dementia process itself.

Neurologists suggest that physical, leisure activities, and mentally stimulating activities, have separate effects in decreasing cognitive decline and reducing Alzheimer's disease risk[41,42]. Studies consistently agree on a significant protective effect of cognitive leisure activities (CLA)[43,44]. Scarmeas et al, in a total of 1,772 non demented individual's aged 65 years or older, living in northern Manhattan, New York, found that the risk of dementia was decreased in people who participated in more leisure activities (RR= 0.62; 95% CI 0.46 to 0.83)[41].

In a Swedish community-based study, the Kungsholmen Project, conducted in 776 subjects, aged 75 years or more who were, cognitively intact at baseline and followed for 6 years (2 waves), it was found that stimulating activity, either mentally or socially oriented, may protect against dementia[45]. Adjusted relative risks for mental, social, and productive activities were 0.54 (95% confidence interval (CI): 0.34, 0.87), 0.58 (95% CI: 0.37, 0.91), and 0.58 (95% CI: 0.38, 0.91), respectively[45].

Wilson et al, in a study 6158 persons aged 65 years and older followed for 4 years, found that a one-point increase in the cognitive activity score was associated with a 64% reduction in risk of incident AD (OR = 0.36; 95% CI 0.20 to 0.65). Conversely, weekly hours of physical activity (mean 3.5; SD 5.1) were not related to disease risk (OR = 1.04; 95% CI 0.98 to 1.10) in a logistic regression model adjusted for age, education, sex, race, and possession of the APOE ε4 allele[46].

The German Interdisciplinary Longitudinal Study on Adult Development and Aging (ILSE)[47], which includes a representative birth cohort of 1002 participants with an average age of 74 years who were cognitively unimpaired at baseline and followed for an average time period of 12 years with three examination waves. Sattler et al found that people with a high cognitive activity score had a reduced risk of developing MCI and AD at time 3 by 62% compared to subjects whose cognitive activity was low at time 1 (OR=0.38, 95% CI 0.15–0.99, P=0.05) after adjusting for sex, education, socioeconomic status and depression[47].

In a longitudinal cohort study in 801 Catholic nuns, priests and brothers aged over 65 years without dementia at enrollment who were recruited from 40 groups across the USA with a mean fellow-up of 4.5 years[48], Wilson et al reported that for each 1-point increase in the cognitive activity score, there was a 33% decrease in the risk of developing AD[48]. To summarize, greater participation in cognitive activities appears to reduce the risk of developing dementia.

II.7. Treatment

II.7.1. Alzheimer's disease:

Available interventions do not cure the disease. Non pharmacologic interventions address behavioural troubles (like environmental modification, minimal excess stimulation, task simplification, etc.) and other possible treatable causes of cognitive impairment such as somatic

illness (e.g. hypothyroidism and anaemia), medication side-effects, modifiable cerebrovascular risk factors (e.g. diabetes, hypercholesterolemia and high blood pressure), psychiatric illness (e.g. depression, heavy drinking) and vitamin deficiency (e.g. B12 and folate)[4].

Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) are approved for the treatment of mild to moderate AD and have been reported to have efficacy. The three available cholinesterase inhibitors in North America are approved for treatment of Alzheimer's disease, not MCI. Many placebo-controlled trials, included participants with mild to moderate dementia and an average age of 74 years, found that the cholinesterase inhibitors are able to slow or to stabilize decline in cognition, function, behaviour and global change compared with placebo[49-68]. Evidence to demonstrate whether one of these drugs is more efficacious than another is limited, although adjusted indirect comparisons suggest that donepezil and rivastigmine may be slightly more efficacious than galantamine. The frequency of adverse events (the most common are nausea, vomiting, diarrhea, dizziness and weight loss) reported in trials, were lowest for donepezil and highest for rivastigmine[69].

Interventions designed to support caregivers in their role such as skills training, education to assist in caring for a person living with dementia can resolve problems including depression and strain, social isolation, financial burden and disruptions to sleep[70].

II.7.2. Mild cognitive impairment

Non pharmacological intervention:

In a randomized trial that used the Cognitive Subscale of the Alzheimer's Disease Assessment Scale to compare the effect of a physical exercise program (brisk walking for 150 minutes per week) with that of usual care and education in persons with subjective memory loss, the exercise group had better cognitive function at 6 months (the primary study outcome), with some residual benefit noted at 18 months[71].

Carter et al found that in stroke patients receiving cognitive skills remediation training mainly in the auditory attention task, followed by visual spatial perception, and correlated significantly with greater improvement in personal hygiene, bathing, and toilet activities. However, recovery in ADL performance depends in part on previous cognitive functioning[72].

In the PAQUID study (n=3,777, aged 65 years or older), regular participation in leisure activities was also found to be associated with a lower risk of subsequent dementia[72,73]. There is thus increasing evidence that staying physically and mentally active reduces the risk of cognitive decline and Alzheimer's disease[41,42].

Pharmacological intervention: Many medications like acethycholinesterases inhibitors (AChEIs) (donepezil, galantamine, rivastigmine) have been studied for an effect on MCI. AChEIs may improve cognitive function and global functioning in the short term with small pooled magnitude changes although they do not yet have government approval. In a randomized clinical trial, Petersen et al found that the donepezil group had a significantly reduced risk of progression to AD during the first 12 months of the study but not at later time points compared with the placebo group[74]. To date, donepezil is the only agent found to delay the progression

from MCI to AD, although the data were derived from a single randomized, placebo-controlled study.

Other medications have also been evaluated such as memantine, low dose aspirin, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (simvastatin and atorvastatin), non-steroidal anti-inflammatory drugs (ibuprofen, naproxen, indomethacin, and celecoxib), gonadal steroids (estrogen with or without progesterone and testosterone), Ginkgo biloba, stimulants such as Ritalin, and dietary supplements (multi-vitamins, vitamin B, vitamin E with or without vitamin C and ω-3 fatty acids)[3]. None of the trials found a benefit for any of these medications or supplements on cognitive or physical function in persons with mild to moderate dementia or MCI nor did they prevent the progression of MCI or AD[75].

There is no current treatment for MCI sufficiently substantiated to have obtained government approval. A patient with MCI should be informed and told of the increased risk of progressing to dementia. The physician should closely follow the patient over time. Reversible causes of memory loss should be investigated and treated[3].

II.8. Relation between eye disease and cognitive decline

II.8.1. The three eye diseases

II.8.1.1. AMD

II.8.1.1.a. Definition

Age-related macular degeneration (AMD) is the leading cause of permanent visual loss in western industrialized countries. Age-related macular degeneration begins by the formation of sub-retinal pigment epithelial yellowish deposits called drusen. Using a modification of the Wisconsin AMD grading system[76], early AMD is characterised clinically by soft drusen accumulations and pigmentary abnormalities in the retinal pigment epithelium (RPE) and Bruch's membrane, whereas late-stage manifestations are defined by atrophy of photoreceptors and the RPE underlying it, choroidal neovascularisation, subretinal haemorrhage, detachment of RPE and retinal scarring[77].

The international consensus classifies late AMD into two well-defined clinical forms: a wet and dry form. Choroidal neovascularization is characteristic of the wet form, a stage found in approximately 20% of cases[78-80]. Although both forms of AMD can cause visual loss, the wet form accounts for approximately 90% of serious visual loss[78-80]. It is also generally accepted that the wet form of AMD follows and arises from the dry form (geographic atrophy). AMD was responsible for 21% of all cases of legal blindness in North America[81].

II.8.1.1.b. Prevalence

According to data from the World Health Organization, AMD is currently considered the third leading cause of blindness worldwide (only behind cataract and glaucoma) and it accounts for 8.7% of blind persons globally[82,83]. The prevalence of AMD is reported to be negligible at age 50 years and approaches 6% at 80 years[84].

In Canada, nearly 1 million individuals currently have early AMD, and approximately 250 000 have advanced forms of the disease[85]. The National Coalition on Vision Health in Canada predict a 111% increase in the incidence of AMD by 2030.

II.8.1.1.c. Risks factors

Older age has been identified as the major risk factor in multiple epidemiological studies. In the Beaver Dam Eye Study[86] (n=4926, aged 43 to 86 years), Rotterdam Study[87] (n=6476, 55-106 years), and Blue Mountains Eye Study (n=4926, 43-86 years)[88], AMD prevalence was strongly age-related. Overall, AMD was present in 0.2% of the combined population aged 55 to 64 years, rising to 13% of the population older than 85 years. Prevalence of neovascular AMD increased from 0.17%, among subjects aged 55 to 64 years, to 5.8% for those older than 85 years[61,62,63].

In the Los Angeles Latino Eye Study (LALES) (n=6357, 49-97 years), prevalence of advanced AMD increased from 0% in those 40–49 years of age to 8.5% in those 80 or older[89]. In the Baltimore Eye Study(n=5308, 40 years or older), age was strongly associated with increasing prevalence of drusen, with rates ranging from about 10% among blacks and whites in their 40s, to over 30% among those in their 80s[90].

Many population-based prospective studies showed that AMD prevalence varied with ethnic background. The Salisbury Eye Evaluation, which included large numbers of both whites and blacks, found that geographic atrophy was more common in whites than in blacks (1.8% compared to 0.3%)[91].

An analysis of the participants in the Multi-Ethnic Study of Atherosclerosis (MESA) (n=6814) showed a prevalence of combined early and late AMD in persons aged 45 years to 85 years to be 2.4% in African Americans, 4.2% in Hispanics, 4.6% in Chinese-decent individuals, and 5.4% in whites[92].

There does not appear to be a gender difference in AMD once age is taken into account although there is a suggestion that neovascular AMD may be more common in women according to a recent meta-analysis[93]. In LALES, there was no significant age-adjusted gender difference in advanced AMD[65].

Smoking is a strong and consistent risk factor for age-related macular degeneration in multiple epidemiological studies. The LALES[89], Beaver Dam[94], Rotterdam[95], Blue Mountains[96] and the Funagata Study[73] studies found a significant association of cigarette smoking for both the early and advanced forms of AMD with statistically significant odds ratios of 2.4, 3.1, and 4.2 for the Beaver Dam, Rotterdam and Blue Mountains populations, respectively[84]. In The Funagata study, current smoking remains highly prevalent among Japanese men (36.8% of

participants in this study), which translates to a 66% population-attributable risk for late AMD cases in Japanese men that are attributable to their smoking behavior[97].

Cardiovascular risk factors (e.g., atherosclerosis[44,46,47], hypertension[98]) have been linked with advanced AMD.

Ocular risk factors for age-related macular degeneration include darker iris pigmentation, previous cataract surgery[61] and hyperopic refraction[60,62,64]. Pooled data from the Blue Mountains and Beaver Dam eye studies found an association between cataract surgery and advanced AMD[99,100], as too did pooled data from the Salisbury Eye Evaluation Survey[101] and the Baltimore Eye Survey[77]. In the Rotterdam study, for each diopter increase in hyperopia (near vision is blurred), there was a 5% increase in the risk of developing incident AMD[102]. Data from cross-sectional studies[102-105] showed that hyperopic eyes are associated with higher odds of AMD, whereas myopic eyes are associated with lower odds of prevalent AMD compared with emmetropic eyes (normal visual acuity).

There is strong evidence for the involvement of genetic factors on the development of age-related macular degeneration. Early studies showed that familial history was a risk factor For AMD. For example, the Beaver Dam Eye Study found that having an older sibling with AMD increased the risk of having AMD in the younger sibling[106]. More recent studies have identified several genes that may play a role in AMD such as ABCA4 (ABCR)[107], FBLN5[108], HEMICENTIN-1 (FBLN6)[109,110], and APOE[111-113]. Very strong evidence exists for the involvement of the complement factor H gene[114,115].

II.8.1.1.d. Treatment of AMD

The use of antioxidant nutrients is protective against progression of dry AMD. This is because oxidative damage from different sources like light exposure, inflammation and local production of reactive oxygen species to the retina has been strongly implicated with AMD. It has been reported in the Age-Related Eye Disease Study Research trial (AREDS) that the AREDS supplements reduce the risk of progression of AMD in people with the dry form of the disease[116]. A systematic review supports the association of dietary lutein/zeaxanthin (LZ) intake and reduced risk of late AMD[117]. The Blue Mountains Eye Study and the Rotterdam Study researchers documented similar findings[118,119].

For the wet form, the two most frequently used drugs are ranibizumab and bevacizumab. Aflibercept has also been recently approved by Health Canada. All of these drugs inhibit vascular endothelial growth factor, which is involved in angiogenesis[120,121].

II.8.1.2. Glaucoma

II.8.1.2.a. Definition

After cataract, glaucoma is the second leading cause of blindness worldwide and the number one cause of irreversible vision loss[122]. Glaucoma is characterized by a distinctive loss

of retinal nerve fibres and optic disc changes with the common feature of an optic neuropathy. Glaucoma can lead to an irreversible loss of visual field, usually beginning paracentrally, and after can progressively affect central visual field[123].

Glaucoma can be divided in two types: open angle or angle closure and the causes can be primary, secondary or congenital.

II.8.1.2.b. Prevalence of Glaucoma and Its Risk Factors

In 2006, the number of individuals estimated to be bilaterally blind from glaucoma was projected to increase from 60.5 million in 2010 to 79.6 million by 2020[122]**.** There are approximately 409 000 people with glaucoma in Canada. A meta-analysis of 5 self-report surveys indicated that the prevalence of glaucoma was 2.7% for Canadians aged 40 years and 11% for those aged 80 years based on data from 2002 and 2003[124].

The prevalence of the various types of glaucoma vary by race/ethnicity.

Primary open angle glaucoma (POAG) alone is responsible for approximately 12% of all blindness in the world and 32% of the blindness in those of African descent[125]. In the United States, 1.9% have POAG[126] while only 0.1% have PACG (primary angle closure glaucoma)[127] in people older than 40 years. The primary risk factors for POAG are elevated intra-ocular pressure (IOP), advancing age, family history of glaucoma, and race.

In the Blue Mountains Eye Study, POAG prevalence was 8.2% in over 80 age group compared with that of the younger age groups[128].

Primary angle closure glaucoma (PACG) is more common in Asian people[100]. As of 2001, it was calculated that 4.5 million people were suffering from PACG in China[129]. Global projections estimate that by 2010 there will be approximately 15.7 million people with PACG, with half of them in China[122].

The risk factors for PACG are axial hyperopia[130], family history of angle closure[131], advancing age[132], female gender[133], race (Asian[134], Latino[127] and Inuit[135] ancestry), shallow peripheral anterior chamber[136] and short axial length of the eye[137]. Women are affected more than men (55% of open angle glaucoma, 70% of angle-closure glaucoma, and 59% of all glaucoma). Refractive error is a risk factor for the 2 types of glaucoma[138,139].

II.7.1.2.c. Treatment of glaucoma

Treatment should be based on the type and cause of glaucoma. The only clinically established method of treating glaucoma is lowering IOP with the identification of a target IOP which needs to be reevaluated and documented at each visit[123]. The effectiveness of IOP lowering in the treatment of glaucoma has been established in several well-designed prospective RCTs.[11,12,48,49] Therapeutic options are the use of topical or systemic medications to lower IOP (beta blockers, alpha-2 adrenergic agonists, and topical carbonic anhydrase inhibitors, miotics

and prostaglandin derivatives), laser trabeculoplasty, surgery to improve outflow facility, and cyclo-destructive laser to reduce aqueous production[123].

II.8.1.3. Fuchs corneal dystrophy

II.8.1.3.a. Definition

Fuchs corneal dystrophy (FCD) is a slowly progressive late-onset disorder. Characteristic features include the formation of focal excrescences of Descemet membrane termed guttae, loss of endothelial cell density and end-stage disease manifested by corneal edema and the formation of epithelial bullae[140]. Patients often present in the fifth to sixth decade of life. It is an inherited autosomal dominant disorder with incomplete penetrance. Women are disproportionately more frequently affected compared to men[140,141].

II.8.1.3.b. Prevalence of Fuchs

Few studies have been performed to assess the prevalence or incidence of this disease. FCD may affect as much as 4% of the American population over the age of 40 years[142] . However, in one genetically isolated population on Tangier Island in Virginia, a sample of half the inhabitants over the age of 50 suggested a prevalence rate as high as 11% [143]. A cross sectional study of 774 participants in the Reykjavik Eye Study in 2005 revealed 11% of females and 7% of males with guttae[144]. An examination of 107 patients with cataract in Japan revealed four (3.8%) with 'primary cornea guttata', described as early signs of FCD[145] . A comparison of

the prevalence of cornea guttata between Japan and Singapore found a significantly increased prevalence of disease in Singapore (8.5 vs 5.5%) and decreased mean endothelial cell counts among its affected individuals relative to Japan[146] .

Some risk factors are cited like UV radiation[144] , smoking history of more than 20 pack-years[144], chronic diseases, axial hypermetropia, shallow anterior chamber angle closure glaucoma[147,148] and AMD[149]. Genetic factors have also recently been identified[150].

II.8.1.3.c. Treatment of Fuchs

The medical treatment of FCD is utilized to treat symptoms of early disease. By increasing external osmolality, hypertonic sodium chloride drops or ointment can be given to extract water from the cornea[140]. To date, definitive treatment requires surgery.

Surgery in FCD is performed for advanced disease. Penetrating keratoplasty has traditionally been the mainstay of surgical treatment, but the recent addition of Descemet stripping endothelial keratoplasty (DSEK) and other endothelial keratoplasties of the cornea offer new alternative procedures that are less invasive[140].

II.8.2. Studies examining relationship between AMD and cognition

Several studies have investigated the relationship between AMD and cognitive impairment or AD with mixed results[151]

In the Rotterdam study, late stage AMD was associated with increased incident AD at 2-year follow-up, after adjusting for age and gender (OR=2.1, 95% CI 1.1, 4.3) but this association was attenuated after adjustment for smoking and atherosclerosis (OR=1.5, 95% CI 0.6, 3.5)[152]. For early AMD, no association was observed in this study. The authors suggested that the relationship between AMD and AD was partially explained by shared cardiovascular risk factors.

Another cross-sectional analysis from the Blue Mountains Eye Study showed that persons with late AMD were more likely to have cognitive impairment, as defined by the Mini-Mental State examination, even after excluding vision related tasks from the examination[36]. However, no association was observed between MMSE and early AMD and a borderline non-significant association of low scores on the modified MMSE (3MSE) with early AMD[151].

The Age Related Eye Disease (ARED) study found that reduced vision due to advanced AMD was associated with worse cognitive function scores as measured by the Modified Mini-Mental State Examination and letter and verbal fluency tasks. (OR = 2.88; 95% CI = 1.75-4.7], after adjustment for age, sex, race, education, smoking status, diabetes mellitus, use of cholesterol-lowering medications, antioxidants, and hypertension.

In the Cardiovascular Health Study, persons with low Digit Symbol Substitution Test (DSST) scores (lowest quartile of scores, ≤30) were more likely to have early AMD (OR = 1.38; 95% CI =1.03-1.85) than persons with higher DSST scores after controlling for age, gender,

race, and center. This association was stronger (OR = 2.00; 95% CI = 1.29-3.10), in analyses further controlling for education, systolic blood pressure, total cholesterol, diabetes, smoking status and APOE genotype[153].

Saido and Iwata[154] report in their review article that ageing of the brain causes abnormal proteolysis, resulting in abnormal deposits of proteins (senile plaque and drusen) followed by progressive neuronal dysfunction and degeneration in AD and AMD patients respectively. These results are supported by Ohno-Matsui[155].

In the ARIC population (aged 45-64 years, n=9286), where standardized protocol to assess AMD signs was used, an association between cognitive impairment, defined as Word Fluency Test scores in the lowest 10% of the population, with early AMD was reported. However, the ARIC study found no association between DSST and early AMD[156].

Proitsi and his colleagues found that there is not an association between well replicated AMD genetic risk factors and AD[157].

The Singapore Malay Eye Study, a cross-sectional population-based study, did not find an association between AMD and cognitive dysfunction[158].

Several biological hypotheses have been proposed to explain the link between AMD and AD:

1) Both diseases have similar histopathological changes[159]. In AMD and AD, there an accumulation of drusen and senile plaque and each containing extracellular β-amyloid.

2) AMD and AD share similar vascular risk factors, such as hypertension, cigarette smoking and stroke.
3) There is evidence of shared genetic loci such as the apolipoprotein E 4 allele, which is positively associated with Alzheimer's disease but inversely with AMD[159].

II.8.3. Studies examining relationship between glaucoma and cognition

Several studies have also investigated the relationship between glaucoma and cognitive status with mixed results. Two case–control studies have shown a higher proportion of glaucoma among AD patients compared to the control participants[160,161].

The strongest support for a relationship comes from The Three-City–Bordeaux–Alienor study, population-based prospective cohort study that showed that participants with an POAG were four times more likely to develop dementia during the 3-year follow-up period (OR = 3.9; 95% CI = 1.5–10.4; p = 0.0054) after adjustment for age, gender, education, family history of glaucoma, vascular comorbidities, and apolipoprotein E4[162]. Dementia was determined by a neurologist.

Clinical data and experiments on human eye tissues have consistently supported common AD and glaucomatous retinal pathology. Histopathologic analyses of enucleated glaucomatous eyes have shown evidence of substantial retinal ganglion cell (RGC) loss

compared to controls, while a higher proportion of patients with AD showed abnormalities in the retinal the nerve fiber layer (NFL)[159].

Other studies investigating a link between glaucoma and cognition have been negative. A retrospective cohort study done using Medicare claims data did not find a relationship between diagnosed glaucoma and Alzheimer's disease[163]. Kessing *et al* also report no association between glaucoma and Alzheimer's disease using a nationwide case register in Denmark[164]. The cross-sectional population-based study of 1179 older adults mentioned above did not find an association between glaucoma and cognitive dysfunction as measured by the Abbreviated Mental Test[158].

To summarize, studies are not in agreement on whether glaucoma and cognitive impairment are related. One possible reason is that up to 50% of glaucoma cases are not diagnosed so studies relying on medical records to diagnose glaucoma may suffer from misclassification to different degrees.

Beyond clinical observations, several biological hypotheses have been proposed to explain a possible link between glaucoma and AD.

1-One is related to an abnormal difference of pressure between cerebrospinal fluid pressure and IOP, that damages the optic nerve[165] .

2-changes in the cerebrospinal fluid composition, particularly in the subarachnoid space of the optic nerve, could lead to abnormal accumulation of proteins (b-amyloid) that have potential toxic effects on optic nerve[166].

3- Some studies have shown that apolipoprotein E 4 allele may be a latent risk factor in the development of primary glaucoma. But these results are controversial with other studies[161,167-170].

4-Other possible mechanisms, such as retinal vessel abnormalities[171] and Helicobacter pylori infection[172], have also been proposed.

II.2.3. Need for further research

There have been limitations in prior research investigating the link between eye disease and cognitive status. Many studies did not include sufficient numbers of people with late AMD or they did not have adequate data on confounders to properly adjust. Many of the glaucoma studies relied on glaucoma diagnoses from a doctor rather than doing eye exams on all participants. Furthermore, results were conflicting.

The research presented in this thesis will significantly add to the existing literature because it used large numbers of patients with late AMD, glaucoma, and Fuchs corneal dystrophy, it used people with normal vision who had comprehensive eye exams as a control population, and it collected data on numerous potential confounders.

CHAPTER III SAMPLE SIZE CALCULATION

For the MMSE-Blind version test, we required 64 people per group in order to detect a difference of 1 unit between groups assuming standard deviations in each group of 2.0, 80% power, and 5% Type 1 error. This calculation was made using PS Power and Sample Size program. Data used for these calculations are based on reasonable assumptions based other literature, and what we believed to be clinically significant differences.

CHAPTER IV RESULTS

Age-Related Eye Disease and Cognitive Function

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ABSTRACT

Purpose : To determine whether people with age-related eye disease have lower cognitive scores than people with normal vision.

Methods : A hospital-based cross-sectional study was performed in which people from the ophthalmology clinics at Maisonneuve-Rosemont Hospital (Montreal, Canada) were recruited who had either age-related macular degeneration (AMD), Fuch's corneal dystrophy, or glaucoma. Controls, recruited from the same clinics, did not have significant vision loss. Cognitive status was measured using the Mini-Mental State Exam Blind Version (range 0-22) which excludes 8 items that rely on vision. Linear regression with bootstrapped standard errors was used to adjust for demographic and medical factors.

Results : People with AMD, Fuch's corneal dystrophy, and glaucoma had lower cognitive scores, on average, than controls ($P<0.05$). These relationships remained statistically significant after adjusting for factors such as age, gender, race, education, living alone, systemic comorbidities, and lens opacity.

Conclusions : People with three different age-related eye diseases had lower cognitive scores. Reasons for this should be explored using longitudinal studies and a full battery of cognitive tests that do not rely on vision.

INTRODUCTION

Cognitive impairment is an acquired deficit in memory, problem solving, orientation, or abstraction. Several epidemiological studies have indicated that people with age-related eye diseases like age-related macular degeneration (AMD) or glaucoma have reduced cognitive scores[1,151,153,158,160,161,173]. Other studies found a null relationship [158,163,164]. Methodological limitations plagued some of the studies such as not having adequate numbers of people with late-stage AMD, lacking a uniform visual exam for cases and controls, or limited adjustment for confounding. In support of the studies that found a positive relationship, there are also biological similarities between eye diseases like AMD and glaucoma, and the major cause of dementia, Alzheimer's disease. Sivak *et al* provide a review of research noting similarities between the three diseases such as retinal damage, amyloid β deposition, pTau, oxidative and metabolic stress, and glial reactivity [159].

Given the lack of consistent epidemiological results on this topic, we examined this issue by recruiting people with one of three age-related eye diseases that differ in which part of the visual system is affected. The three eye diseases that we included were AMD, glaucoma, and Fuch's corneal dystrophy. We hypothesized that all three groups would have worse cognitive scores than our control group with normal vision after adjusting for potential confounders.

METHODS

Study Design and Population

All participants were recruited from the ophthalmology clinics of Maisonneuve-Rosemont Hospital in Montreal, Canada between September, 2009 and September, 2013. Research personnel reviewed patient files each day for 5 retinal specialists, 5 glaucoma specialists, 4 corneal specialists, and 6 general ophthalmologists to check for eligible patients who were then approached in the waiting room regarding participation. It is a sub-study from mobility study. This study was not designed to evaluate cognition as a primary outcome. To be eligible for this cross-sectional study, participants had to be 65 years or older. Participants had to have either no significant vision loss (controls) or one of three age-related eye diseases: age-related macular degeneration (AMD), Fuch's corneal dystrophy, or glaucoma. Each group had to meet certain visual criteria as well. The AMD and Fuchs patients were required to have bilateral disease and to have visual acuity of worse than 20/40 in their better eye. Glaucoma patients were required to have bilateral disease and to have a visual field mean deviation worse than or equal to -4dB in their worse eye. This would be considered "early" visual field loss according to prior literature[174]. All glaucoma types were recruited. The 3 groups with eye disease were allowed to have other eye diseases, which may have also impaired vision. However, a person was not included if he/she met the visual inclusion criteria for multiple groups (i.e. AMD and Fuchs). Finally, the controls were required to have visual acuity of 20/40 or better in the better eye and a visual field mean deviation in the worse eye better than -4dB. Controls either had no current eye disease (67%) or they had non-visually impairing conditions such as early

cataract (15%), early AMD (3%), ocular hypertension (5%), blepharitis (3%), or other (6%). People who had received eye surgery, laser, or an intra-vitreal injection in the last 3 months were enrolled after a 2-3 month delay so that their data would be less affected by their treatment and recovery.

There were 776 people who appeared to meet eligibility criteria from a review of the medical records. Of the 776 people, 518 (67%) people accepted our invitation to be in the study, 208 (27%) refused, and 50 (6%) were not capable of responding for themselves. Of the 518 who accepted, 420 people met final eligibility criteria including 113 with age-related macular degeneration (AMD), 130 with glaucoma, 66 with Fuch's corneal dystrophy, and 111 people without significant eye disease. Participants were paid $10 for their participation and signed a consent form. The project was approved by the Ethics Committee of the Hospital and the research conformed to the tenets of the Declaration of Helsinki.

Data Collection

Data were collected from questionnaires, vision tests, and a review of the medical record.

Cognitive status was measured using the Mini-Mental State Exam (MMSE) Blind Version which was validated by Busse et al [9]. The Blind Version omits 8 items that directly or indirectly rely on vision. The MMSE Blind Version is a global test of cognition. Participants with scores less than 17 meet the criteria for cognitive impairment [9]. Demographic information was collected on age, gender, ethnicity, and highest grade of education. Participants were asked

if they lived alone and about the presence or absence of a physician diagnosis of 13 chronic conditions such as diabetes, heart disease, arthritis, asthma, chronic obstructive pulmonary disease, hypertension, chronic arterial insufficiency, stroke, Parkinson disease, depression, hearing loss, spine disease and hip fracture.

Visual acuity was tested using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart with illuminated light box at 2 meters or at 1 meter if the participant could not read any letters at 2 meters[175,176]. Letter by letter scoring was performed with scores at 2 meters converted to scores at 1 meter by adding 15. Scores were converted to logMAR. Contrast sensitivity was measured using the Pelli-Robson chart at 1 meter for each eye [177]. Forced choice letter-by-letter scoring procedures were used until a participant read all 3 letters of a triplet incorrectly. Visual field was measured using the Humphrey FDT test with full threshold N-30 testing in each eye [178]. The FDT measures 30˚ horizontally and 24˚ vertically.

The medical record was reviewed and further detail on the patient's eye disease and any coexisting eye disease (such as lens opacity) was recorded. Those who could not perform the FDT test because of advanced eye disease had their last visual field exam results taken from the medical record.

Statistical Analysis

The primary outcome was the continuous score from the MMSE Blind test. The mean MMSE Blind scores were compared between the four groups (AMD, Fuchs, glaucoma, control) by the ANOVA test. Multiple linear regression was used to determine whether the groups with eye disease had worse cognitive scores adjusting for demographic and health factors that were considered potential confounders. Standard errors and 95% confidence intervals for the regression estimates were obtained from bootstrapping (2000 replicates) [179]. Analyses were done in Stata Version 11.0 (College Station, Texas).

RESULTS

We enrolled 420 people who resided in the community (82%), assisted living facilities (8%), and retirement homes (10%). Characteristics of the four groups are shown in Table 1. The groups with age-related eye disease were older, had less education, and had more systemic comorbidities than the control group ($P<0.05$). The AMD and Fuchs groups had a greater percentage of women than the control group ($P<0.05$). The mean visual acuity of the AMD and Fuchs groups was 20/100 and 20/80 respectively. The mean visual field mean deviation in the better eye in the glaucoma group was –9.5dB.

The mean MMSE Blind scores were lower in the three groups with age-related eye disease than in the control group ($P<0.001$). Also, a greater percentage of people in the groups with eye disease had cognitive impairment compared to the control group ($P=0.019$).

After adjustment for demographic and health factors (Table 2), all three groups with age-related eye disease had lower MMSE Blind scores than the control group ($P<0.05$). The scores, in AMD, Fuch's and glaucoma group, were 0.81, 0.82 and 0.72 lower than the control group, respectively. Other factors that were associated with worse cognition included older age, being of African descent, and living alone ($P<0.05$). Better education was associated with better cognition ($P<0.001$).

In Table 3, we examined which measures of visual function were most strongly related to cognitive function. Contrast sensitivity and visual acuity were highly statistically significant ($P<0.001$, CI = (0.69, 2.1) and CI = (-2.11, -0.06) respectively) while visual field in the better eye had borderline statistical significance ($P=0.09$, CI = (-0.01, 0.08)). The placement of all three measures of visual function in the model together results in the loss of statistical significance for all three due to their colinearity.

DISCUSSION

All three of the groups with age-related eye disease had lower cognitive scores when compared to a control group with good vision. This is despite the fact that the three diseases all

affect different parts of the eye, leading one to believe that the relationships may not primarily be due to common pathogenesis[159]. An alternative explanation is that the loss of vision at an older age leads to a lack of cognitive stimulation that over time is harmful to the brain. In fact, numerous observational studies have shown that participation in cognitively stimulating activities decreases the risk of cognitive impairment[48,180,181]. Furthermore, randomized clinical trials have found that cognitive training programs can improve cognitive function[182,183]. However, cognitive training programs typically require good vision and many cognitively stimulating leisure activities also require good vision or adapted materials (e.g. reading, playing cards, driving) making it difficult for people with vision loss to participate. In fact, studies have found that older adults with lower levels of visual acuity have reduced levels of leisure-time physical activity[184,185].

Our results showing that glaucoma and Fuch's corneal dystrophy are related to reduced scores on the MMSE Blind version are novel, to our knowledge. Our results confirm findings from the Blue Mountains Eye Study, which also found that people with late AMD had lower scores on the MMSE minus 5 items that relied on vision (the MMSE Blind Version that we used omits 8 items)[151]. The MMSE is a global cognitive test that was designed to detect dementia rather than to evaluate the full range of cognition for research purposes. Therefore, it suffers from a ceiling effect when used in populations who are relatively free of dementia. Future studies should use a variety of cognitive tests that evaluate different domains of cognition and that can finely differentiate cognition in primarily non-demented people. Longitudinal studies are needed to establish the temporality of the vision loss relative to the cognitive decline.

A strength of this study is that we had relatively large numbers of people with eye disease compared to the population-based studies that have previously been done. Furthermore, our controls were recruited from the same clinics as the people with eye disease which helps to ensure their similarity. In fact, the mean full scale MMSE score in our controls was 28 (SD=1.6), which is identical to people of a similar age in population-based studies [186]. Limitations include that our data are cross-sectional, that we only had a single cognitive test, and that we do not have data on certain potentially important confounders like smoking, diet, genetic factors, and atherosclerosis. Future studies should include these factors.

Reasons why age-related eye disease and cognitive decline are related need further investigation. Cognitive decline is a major risk factor for admission to nursing home facilities and a major cost to society[187,188], and on top of visual impairment, would be doubly disabling. Efforts to better understand and prevent cognitive decline in people with poor vision are necessary.

TABLES

Table I : Description of eye disease and control groups

	AMD Mean (SD) or % n=113	*Fuch's Mean (SD) or % n=66*	*Glaucoma Mean (SD) or % n=130*	*Controls Mean (SD) or % n=111*	*P-value**
Demographics					
Age	82.5 (6.4)	78.5 (7.1)	76.6 (7.6)	74.0 (4.9)	<0.001
Female gender	75%	83%	58%	59%	<0.001
Ethnicity					
Caucasian	100%	100%	89%	97%	0.001
African descent	0%	0%	11%	3%	
Education, years	9.4 (3.4)	10.9 (4.5)	10.9 (4.2)	11.8 (3.7)	0.001
Live Alone					
Yes	53%	41%	32%	39%	0.008
No	47%	59%	68%	61%	
Eye measures:					
Binocularvisual acuity, logMAR	0.71 (0.40)	0.59 (0.31)	0.27 (0.29)	0.04 (0.06)	<0.001
Logcontrast sensitivity in better eye, letters correct	1.09 (0.41)	1.16 (0.34)	1.29 (0.34)	1.80 (0.15)	<0.001

Visual field in better eye, MD in dB	-3.1 (3.7)	-2.9 (3.6)	-9.5 (6.6)	0.5 (2.0)	<0.001
Lens Opacity	29%	26%	28%	15%	0.057
Cognitive measures					
Mini-Mental Blind Version (max 22)	19.1 (2.6)	19.7 (2.6)	19.3 (2.9)	20.7 (1.4)	<0.001
Cognitive Impairment	14%	14%	12%	3%	0.007
Comorbidities					
Number of Comorbidities	3.3 (1.9)	2.9 (1.9)	2.6 (1.6)	2.0 (1.5)	<0.001

* P-value derived from ANOVA for continuous variables or chi-square test/Fishers exact test for categorical variables

Table II: Relationships between age-related eye disease and cognitive status from linear regression model

	Cognition	
	β	**Bootstrapped 95% CI**
Eye Disease Group		
Control	0.00	
AMD	-0.81	-1.44, -0.17
Fuch's	-0.82	-1.49, -0.15
Glaucoma	-0.72	-1.23, -0.20
Age	-0.06	-0.10, -0.03
Gender		
Male	0.00	
Female	0.46	-0.06, 0.97
Ethnicity		
Caucasian	0.00	
African descent	-2.25	-3.80, -0.70
Education	0.21	0.14, 0.27
Live Alone	-0.61	-1.05, -0.16
Number of Comorbidities	-0.00	-0.14, 0.14
Lens Opacity	0.10	-0.44, 0.65

Table III : Multiple linear regression models showing adjusted relationship between three measures of visual function and cognitive status

Model	*Visual Function Variable*	*Cognitive Status*	
		β	*95% CI*
Model 1*	Binocular Logmar Acuity, per 1 unit	-1.09	-2.11, -0.06
Model 2*	Log Contrast Sensitivity, per 0.1 unit	1.40	0.69, 2.10
Model 3*	Visual Field in Better Eye, per dB	0.04	-0.01, 0.08

*All models also adjusted for age, gender, ethnicity, education, number of comorobidities, living alone, and lens opacity.

CHAPTER V DISCUSSION

V.1. Eye disease and cognitive decline

All three groups with eye disease had lower cognitive scores than people with normal vision. There was not much difference in cognitive scores between those who had central vision loss due to AMD or Fuchs compared to those who had more peripheral vision loss due to glaucoma. Therefore, the type of vision loss did not seem to matter as much as the loss of vision itself regardless of its location. When we looked at the relationships between measures of visual function and cognition, the strongest relationship was found with contrast sensitivity followed by visual acuity and visual field.

On average, the magnitudes of the lower cognitive scores were modest at about 0.7 to 0.8 units on the MMSE Blind version after adjustment. However, it is important to remember that the MMSE-Blind has a ceiling effect so the difference might be much greater using a test that has a greater range of values on the higher functioning end. Furthermore, there were large differences in the percentages of people who had cognitive impairment, defined as a MMSE-Blind score less than 17, as only 3% of those with normal vision had cognitive impairment compared to over 10% in those with each of the eye diseases.

V.2. Strengths and limits of the study

This study was novel in its recruitment of patients with three different eye diseases compared to a control group with good vision. No studies have been done to examine the relationship between eye diseases like glaucoma or Fuchs with cognitive function using the MMSE Blind version test. Cognitive function was measured by MMSE-Blind version test, which was validated by Busse et al against the full version. The test did not rely on vision because it omits 8 items that require image processing in a test situation (range 0-22). Data on potential confounders such as age, gender, ethnicity, living alone, comorbidities, education and lens opacity were also collected and included in the analysis. All potential patients were recruited from the same clinics and response rate was recorded. There was a representative sample of eligible patients from the clinic. There was a 67 % response rate in this study.

There are some limitations of the study. Because it was cross-sectional, one cannot make any assumptions regarding the temporality of the onset of eye disease and the onset of cognitive decline. A longitudinal design would have offered more insight in ascertaining the temporal order of circumstances surrounding the cognitive impairment. One concern about the inability to show temporality is the risk of reverse causality. It was hypothesized that patients with eye disease might reduce their stimulating activities because of their vision, leading to cognitive decline. However, it is also possible that patients who develop cognitive impairment due to other factors then go on to develop more severe eye disease due to an inability to properly care for the eyes. Many studies have questioned whether AMD, glaucoma and cognition might share the same biological mechanisms (e.g. genes, abnormal protein deposits)[159] and have discussed the

common mechanisms that can underlie all three diseases, with potential use of the retina as a biomarker for AD diagnosis and progression[189,190]. So, they can coexist together and be latent until the patient or the physician discovers the pathology. This is why longitudinal data are needed to properly establish temporal relationships.

No data on cognitively stimulating activities, on smoking and on genetic factors is another limitation as these factors may help to explain reduced cognitive function in people with eye disease. Finally, another limitation was that this study was designed to examine mobility as a primary outcome-not cognition. Therefore, only one cognitive test was used which is a global test of cognitive function, has limited sensitivity to detect MCI, and has a ceiling effect in the highest value scores.

V.3. Clinical implications and future research

This study is a first step in trying to understand the link between eye disease and cognitive function. The next steps will be to undertake longitudinal studies to better understand why this link exists. Longitudinal studies should include both biological and social factors to fully understand this link. Once we understand why eye disease and cognitive function are related, then we can educate patients about this risk and help them take steps to reduce their risk of cognitive decline. Currently, cognitive training programs require good vision to use them so they are of little help to people with low vision.

This work and subsequent work on this topic is important patients, their families, their physicians, and low vision rehabilitation providers. Patients with eye disease may benefit from

knowledge that their cognitive function may be affected and that they need to monitor their cognitive health and take steps to improve it. Families of patients may also find this research beneficial. They may take steps to make the living environment of the patient with eye disease more stimulating. Finally, rehabilitation providers may find this study useful in order to develop interventions that do not rely on vision to prevent cognitive decline. Moreover, older adults with eye disease may benefit from a comprehensive geriatric evaluation and the elaboration of a treatment plan to address modifiable non-visual risk factors for cognitive problems like benzodiazepine use.

This study is the first step for future longitudinal investigations to examine the trajectory of cognitive function over time and to understand the reasons for reduced cognition in people with eye disease.

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Table IV: Some cognitive tests used in research

Measure	Description/ rationale	Criterion
MMSE (Folstein, 1975)[6]	Measure orientation to time and place, memory, attention, calculation, language and visual construction	Total score max = 30
MMSE Blind Version (Reischies and Geiselmann, 1997)[8]	Measure orientation to time and place, memory, attention, calculation, and language.	Total score max = 22
the General Practitioner Assessment of Cognition (GPCOG), (Brodaty et al., 2002)[191]	Patient section measure time orientation, clock drawing, information and memory recall and informant section consist of eight historical questions	Patient section: maximum score = 15 Informant section (maximum score = 8).
Memory Impairment Screen (MIS), (Buschke 1999)[10]	Measure word-recall task that tests encoding as well as retrieval	
The Abbreviated Mental Test (AMT) (Hodkinson, 1972)[192]	Measure orientation semantic knowledge episodic memory delayed recall, picture naming and attention.	Max score = 10
Modified Mini-Mental State Examination(3MSE), (Teng et al., 1987)[193]	Measure orientation, concentration, language,	Max score = 100.37

	praxis and immediate and delayed memory	
The Cambridge Mental Disorder OF Eldery Examination (CAMDEX–Section H) (Roth et al., 1986)[194]	Structured interview with the participant's significant Other (i.e., informant) addressing the subject's history 1. Memory changes 2. Changes in general mental function	Yes, No
WMS Information (Wechsler, 1974)[197]	Measure of long-term recall	Max score = 6
Buschke Cued Memory Paradigm (Buschke, 1984; Tuokko and Crockett, 1989)[195,196]	Measure of short-term memory; free and cued recall conditions 1. Free recall: Trial 1 2. Total cued recall: Sum of cued recall trials 1–3 3. Total free recall: Sum of free recall trials 1–3	Total score; Max scores: Free = 12; Total cued = 36; Total free = 36
WAIS-R Block Design (Wechsler, 1981)[197]	Measure of visuospatial ability, construction, and motor function (short version [items 1–9]; odd items only)	Total score; Max score = 30
WAIS-R Similarities (Wechsler, 1981)[197]	Measure of abstract thinking and verbal	Total score; Max score = 14

	problem-solving (short version [items 1–13]; odd questions only)	
WAIS-R Comprehension (Wechsler, 1981)[197]	Verbal measure of judgment (short version [items 1–15]; odd questions only)	Total score; Max Score = 15
Rey Auditory-Verbal Learning Test (Rey, 1941)[198]	Measure of short-term verbal memory 2 1. List A: Trial 1 2. List A: Trial 6 3. Total recall list A: Sum of trials 1–5	Total score; Max scores: Trials 1 ¼ 15; Trial 6 ¼ 15; Total ¼ 75
Controlled Oral Word Association Test (Spreen, 1977 and Benton, 1969)[199]	Measure of verbal fluency and cognitive flexibility (total number of words generated for words beginning with the letters F, A, and S).	
Benton Visual Retention Test (MC; Benton, 1974)[200]	Measure of nonverbal memory	Number correct; Max Score = 16
WAIS-R DIGIT Symbol Test (Wechsler, 1981)[197]	Measure of attention, problem-solving, and processing speed	Max Score = 93

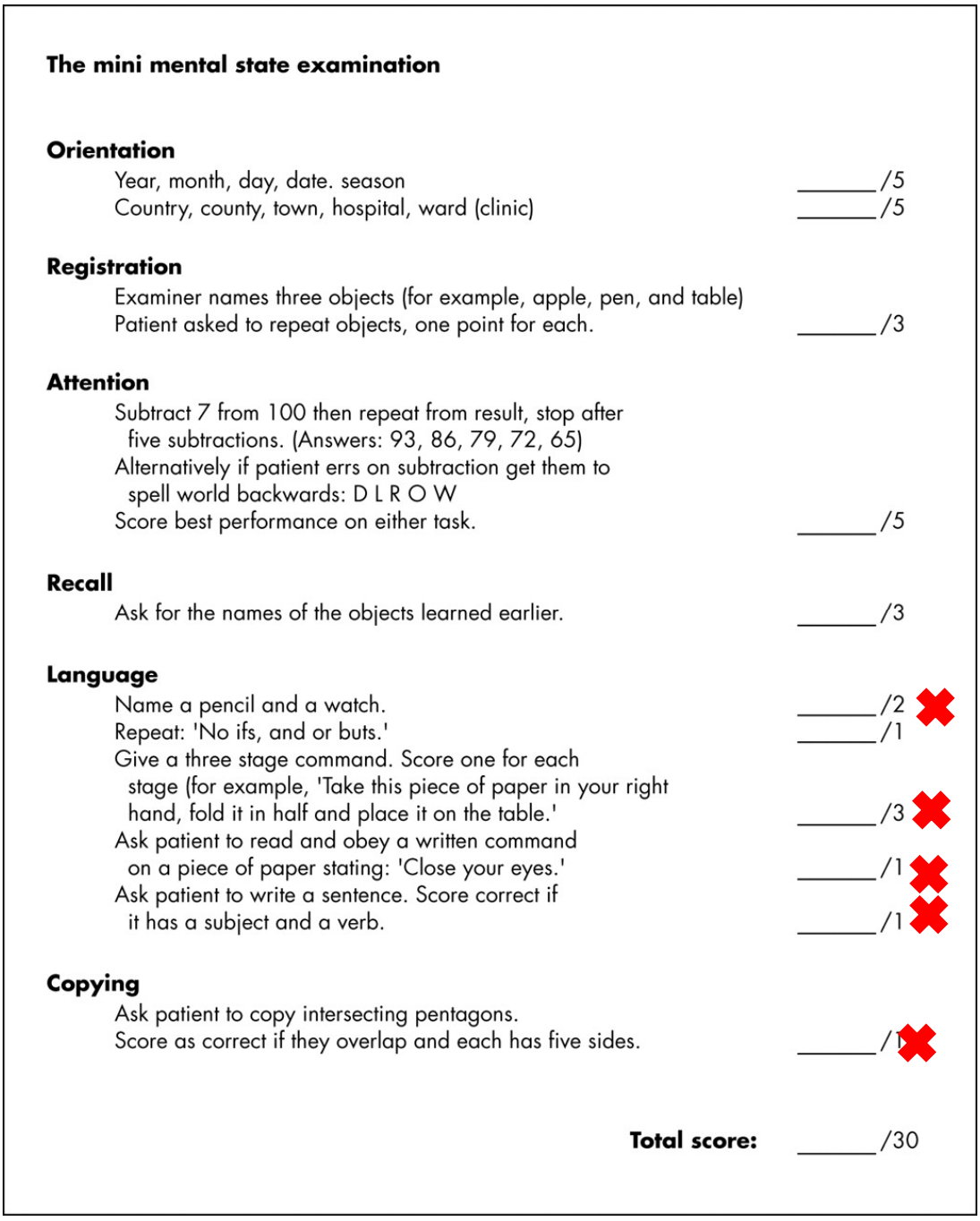
MoCA, (Yeo et al., 1997), Nasreddine et al., 2005) (Dong *et al.*, 2010)[18].	Measure seven cognitive domains, both memory (verbal memory and visual memory) and the non-memory domains (attention, language, visuomotor speed, visuoconstruction and executive function)	Max score = 29
The Trail Making Test, Part A(Spreen and Strauss 1998)[201]	Measure the speed of processing that involves visual scanning and psychomotor speed	Time limit = 300 s
The Clock Drawing test (Goodglass and Kaplan 1983)[202]	Measure semantic memory related time, number and/or linguistic facility and visual motor processing	Max score = 6 points

Table V: The frequency of CIND and dementia and the measurement tools used from large population-based studies throughout the world

Population based study	Cognitive measurement	CIND %	Dementia %
The Italian Longitudinal Study of Aging (n=3,425, 65-84 years)[26]	MMSE, CAMDEX section B and H, the Pfeffer Functional Activities Questionnaire, a neurological examination, review of clinical record.	10.7	-
The Canadian Study of Health and Aging (CSHA) (N=10,263, >65 years)[3,25]	100-point scale modified version of the 3MSE	16.8	8
In the Kungsholmen project >75 years[27,28]	-MMSE (CIND) - Phase I: MMSE, Katz index of ADL Phase II: Clinical examination, MMSE, ADL(dementia)	(n=1,435) 14.7	(n=1,810) 5
Taiyuan Study (n=6,192, >65 years)	MMSE, Boston Naming Test, Trail Making Tests A and B, Block Design, Rey Auditory Verbal Learning Test, Visual Reproduction, Logical Memory, letter and category fluency, the National Adult Reading Test, the Geriatric Depression Scale, and the ‘‘state’’ section of the State-Trait Anxiety Inventory	9.7	-

the Cardiovascular Health Study > 65 years	Modified Mini-Mental State Examination (3MSE) 16 and Digit Symbol Substitution Test (DSST).	8.5	19.6

Figure 1: Mini-Mental Status Exam Blind Version – English Version



The mini mental state examination

Orientation

Year, month, day, date. season _____/5
Country, county, town, hospital, ward (clinic) _____/5

Registration

Examiner names three objects (for example, apple, pen, and table)
Patient asked to repeat objects, one point for each. _____/3

Attention

Subtract 7 from 100 then repeat from result, stop after five subtractions. (Answers: 93, 86, 79, 72, 65)
Alternatively if patient errs on subtraction get them to spell world backwards: D L R O W
Score best performance on either task. _____/5

Recall

Ask for the names of the objects learned earlier. _____/3

Language

Name a pencil and a watch. _____/2
Repeat: 'No ifs, and or buts.' _____/1
Give a three stage command. Score one for each stage (for example, 'Take this piece of paper in your right hand, fold it in half and place it on the table.' _____/3
Ask patient to read and obey a written command on a piece of paper stating: 'Close your eyes.' _____/1
Ask patient to write a sentence. Score correct if it has a subject and a verb. _____/1

Copying

Ask patient to copy intersecting pentagons.
Score as correct if they overlap and each has five sides. _____/1

Total score: _____/30

Figure 2 : Mini-Mental Status Exam Blind Version – French Version

ORIENTATION

Je vais vous poser quelques questions pour apprécier comment fonctionne votre mémoire.
Les unes sont très simples, les autres un peu moins. Vous devez répondre du mieux que vous pouvez.

Quelle est la date complète d'aujourd'hui ? _____

■ Si la réponse est incorrecte ou incomplète, posez les questions restées sans réponse, dans l'ordre suivant :

1. **En quelle année sommes-nous ?** ☐
2. **En quelle saison ?** ☐
3. **En quel mois ?** ☐
4. **Quel jour du mois ?** ☐
5. **Quel jour de la semaine ?** ☐

■ Je vais vous poser maintenant quelques questions sur l'endroit où nous nous trouvons.

6. **Quel est le nom de l'hôpital où nous sommes ?** ☐
7. **Dans quelle ville se trouve-t-il ?** ☐
8. **Quel est le nom du département dans lequel est située cette ville ?** ☐
9. **Dans quelle province ou région est situé ce département ?** ☐
10. **A quel étage sommes-nous ici ?** ☐

APPRENTISSAGE

■ Je vais vous dire 3 mots ; je voudrais que vous me les répétiez et que vous essayiez de les retenir car je vous les redemanderai tout à l'heure.

11. Cigare		Citron		Fauteuil	☐
12. Fleur	ou	Clé	ou	Tulipe	☐
13. Porte		Ballon		Canard	☐

Répéter les 3 mots.

ATTENTION

■ Voulez-vous compter à partir de 100 en retirant 7 à chaque fois ?

14. 93 ☐
15. 86 ☐
16. 79 ☐
17. 72 ☐
18. 65 ☐

■ Pour tous les sujets, même pour ceux qui ont obtenu le maximum de points, demander :
Voulez-vous épeler le mot MONDE à l'envers : E D N O M

RAPPEL

■ Pouvez-vous me dire quels étaient les 3 mots que je vous ai demandés de répéter et de retenir tout à l'heure ?

19. Cigare		Citron		Fauteuil	☐
20. Fleur	ou	Clé	ou	Tulipe	☐
21. Porte		Ballon		Canard	☐

LANGAGE

■ Montrer un crayon.

22. **Quel est le nom de cet objet ?** ☐

■ Montrer votre montre.

23. **Quel est le nom de cet objet ?** ☐

24. **Écoutez bien et répétez après moi : «PAS DE MAIS, DE SI, NI DE ET»** ☐

■ Poser une feuille de papier sur le bureau, la montrer au sujet en lui disant :
«Écoutez bien et faites ce que je vais vous dire :

25. **Prenez cette feuille de papier avec la main droite,** ☐
26. **Pliez-la en deux,** ☐
27. **Et jetez-la par terre.»** ☐

■ Tendre au sujet une feuille de papier sur laquelle est écrit en gros caractères :
«FERMEZ LES YEUX» et dire au sujet :

28. **«Faites ce qui est écrit».** ☐

■ Tendre au sujet une feuille de papier et un stylo, en disant :

29. **«Voulez-vous m'écrire une phrase, ce que vous voulez, mais une phrase entière.»** ☐

PRAXIES CONSTRUCTIVES

■ Tendre au sujet une feuille de papier et lui demander :

30. **«voulez-vous recopier ce dessin»** ☐

SCORE TOTAL (0 à 30) : ☐☐