Myopia and Cognitive Dysfunction: The Singapore Malay Eye Study

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Purpose. To investigate a possible relationship between refractive error and cognitive function.

Methods. This population-based, cross-sectional study included 1032 persons aged 60 to 79 who participated in the Singapore Malay Eye Study. Refraction (sphere, cylinder, and axis) was measured using an autorefractor, and spherical equivalent was defined as sphere plus half negative cylinder. Refractive errors were defined as myopia (spherical equivalent < -0.5), emmetropia (-0.5 diopter [D] $\leq$ spherical equivalent ≤ 0.5 D), and hyperopia (spherical equivalent > 0.5 D). Visual acuity was measured with a logMAR chart. Cognitive dysfunction, assessed using the Abbreviated Mental Test, was defined based on education-specific cutoff values.

Results. Compared with individuals with emmetropia, persons with myopia were almost twice as likely to have cognitive dysfunction (odds ratio 1.82; 95% confidence interval 1.05–3.15), after adjusting for age, sex, body mass index, income, education, and hours of reading and writing per day. Hyperopia was not associated with cognitive dysfunction. The association remained significant after further adjustment for uncorrected refractive errors or best-corrected visual acuity.

Conclusions. Our results provide evidence on a novel association between myopia and cognitive dysfunction. (*Invest Ophthalmol Vis Sci.* 2013;54:799–803) DOI:10.1167/iovs.12-10460

Refractive errors and cognitive impairment are common conditions in older adults.[1,2] Previous studies have reported that impaired visual acuity is an independent risk factor for cognitive decline.[3,4] Uncorrected refractive errors are the main cause of visual impairment,[5] but possible relationships between refractive errors and cognitive dysfunction have not yet been examined.

There are several lines of evidence that suggest a possible association between refractive errors and cognitive dysfunction. First, the incidence and severity of uncorrected refractive errors increases with age,[6] and the resulting poor vision from inadequate correction may increase the risk for cognitive dysfunction. Second, similar pathological alterations may be present in both myopia and cognitive impairment. β-amyloid deposits, a precursor of cognitive decline, have also been found in the crystalline lens, which potentially increases its thickness and curvature, leading to a "myopic shift."[7,8] In contrast, myopia is strongly correlated with higher education and reading ability, which in turn could potentially reduce the risk of cognitive dysfunction.[9,10]

We are unaware of studies that have directly examined a possible relationship between refractive errors and cognitive function. Thus, the purpose of our study was to examine the relationship between refractive errors and cognitive dysfunction in a population-based sample of adults aged 60 to 79 years.

Materials and Methods

Participants

Participants were community-dwelling Malay adults aged 40 to 79 years from the Singapore Malay Eye Study (SiMES), a population-based, cross-sectional epidemiologic study of 3280 urban Malay adults. Only persons who were 60 years and older underwent cognitive screening and were included in this study. Of the 2149 eligible persons aged 60 to 79 years, 1478 participated from 2004 to 2006. The overall participation rate was 76.1%. The response rates by age and sex were 76.5% and 77.2% in males aged 60 to 69 years and 70 to 79 years, respectively, and 78.0% and 72.0% in females aged 60 to 69 years and 70 to 79 years, respectively. Study design and population details have been described elsewhere.[11]

All study procedures were performed in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from the participants, and the study was approved by the institutional review board of the Singapore Eye Research Institute.

Refraction Measurement

Noncycloplegic refraction was used in this study. Each participant's refractive error was obtained with an autorefractor machine (Canon RK-5 Auto Ref-Keratometer; Canon, Inc., Ltd., Tokyo, Japan). Subjective refraction was performed by a trained, certified study optometrist to achieve best-corrected visual acuity. Spherical equivalent was calculated as sphere plus half negative cylinder. Myopia was defined as spherical equivalent less than -0.5 diopter [D] in either eye, emmetropia was defined as spherical equivalent between and including -0.5 D and 0.5 D, and hyperopia was defined as spherical

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equivalent greater than 0.5 D.[12] In supplementary analysis, an alternative definition of myopia as spherical equivalent less than –0.75 D was also used for analysis.[13]

Visual Acuity

Visual acuity was measured using the logarithm of the minimum angle of resolution (logMAR) number chart (Lighthouse International, New York, NY) at a distance of 4 meters with the participant wearing their presenting optical correction, or after best correction of refraction. Visual impairment was defined using best-corrected or presenting visual acuity, as the logMAR greater than 0.3 in the better-seeing eye (US definition).[14] Uncorrected refractive error was defined as at least a two-line difference between presenting and corrected logMAR in either eye.[15] As visual impairment is related to cognitive dysfunction,[16] we excluded persons with visual impairment despite best correction of refraction.

Assessment of Lens Opacity and Age-Related Macular Degeneration

In older adults, the development of lens opacity is often accompanied by changes in refractive index,[17] hence we also tested for associations between cataract and cognitive dysfunction. Cataracts were assessed from digital lens photographs using the Wisconsin Cataract Grading System[18] and defined as nuclear cataract opacity greater than or equal to 4%, cortical cataract greater than or equal to 25%, or posterior subcapsular cataract greater than or equal to 5%.[19] The presence of age-related macular degeneration (AMD) was graded from retinal photographs according to the Wisconsin Age-Related Maculopathy Grading system.[20]

Assessment of Cognitive Status

The Abbreviated Mental Test (AMT) is a 10-question test of general cognitive function, derived from the Hodkinson's Test.[21] Items assess orientation (3 points), semantic knowledge (1 point), episodic memory (3 points), delayed recall (1 point), picture naming (1 point), and attention (1 point). The AMT was interviewer-administered in English or Malay, in accord with the participant's preference, to all SiMES participants aged 60 years and older. The education-based cutoff scores for the AMT have previously been validated against the Mini-Mental State Examination. For subjects with 0 to 6 years of formal education, the previously established cutoff score was 6, with a sensitivity of 89.6% and specificity of 92.6%. For subjects with more than 6 years of formal education, the cutoff score was 8, with a sensitivity of 82.1% and specificity of 92.9%.[22] In this study, cognitive dysfunction was defined as a score less than or equal to 6 of 10 for those with 0 to 6 years of formal education, and less than or equal to 8 of 10 for those with more than 6 years of formal education.[16]

Assessment of Other Risk Factors

Participants underwent a standardized interview for socioeconomic measures (e.g., personal income, education), lifestyle risk factors (e.g., smoking, number of hours spent reading and writing per day), medication use, and self-reported history of systemic diseases (e.g., history of stroke). Nonfasting venous blood samples were analyzed at the National University Hospital Reference Laboratory for biochemical testing of serum total cholesterol and glycosylated hemoglobin (HbA1c). Hyperlipidemia was defined as total cholesterol of 6.2 mM or more, or a self-reported history of lipid-lowering medication use. Hypertension was defined as systolic blood pressure 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater, or use of antihypertensive medication. Diabetes was defined as random glucose 11.1 mM or greater, use of diabetic medication, or a physician diagnosis of diabetes. Current smokers were defined as those currently smoking any number of cigarettes (i.e., current versus past/never). Previous stroke was ascertained from self-report. Body mass index (BMI) was calculated as body weight (in kilograms) divided by body height (in meters) squared.

Statistical Analysis

Statistical analysis was performed using STATA version 11.0 (StataCorp, College Station, TX). Age-sex-adjusted and multivariable logistic regression models were used to determine the relationship of refractive error categories (exposures) with cognitive dysfunction (outcome). The potential confounders considered were age, sex, BMI, hyperlipidemia, diabetes, HbA1c level, hypertension, history of stroke, smoking status (current versus past/never), the presence of AMD and cataract, number of hours of reading and writing per day (none, 0.1 to 2 hours, >2 hours to 5 hours, >5 hours), income category (<SG $1000, SG $1000 to <$2000, SG $2000 to <$3000, >3000), and education level (no formal education, <6 years of education, completed 6 years of education, high school, college or higher).[23] Statistically significant confounders were determined using manual backward elimination procedures with P greater than 0.20 criterion for elimination. In other multivariable models, we further adjusted for uncorrected refractive errors (Model 3) and best-corrected visual acuity in the better eye in logMAR units (Model 4), in addition to the variables not eliminated by backward stepwise procedure. In supplementary analysis, analyses were repeated using an alternative definition of myopia as spherical equivalent less than –0.75.

Results

We excluded 305 persons with missing cognitive testing and 172 persons with visual impairment data. This left 1032 participants (68.4% of those aged 60 to 79 from SiMES) for the final analysis.

Table 1 summarizes the demographic characteristics of the study participants based on cognitive dysfunction status. Persons with cognitive dysfunction were more likely older, female, less likely current smokers, had higher high-density lipoprotein (HDL) cholesterol levels, lower education attainment, less income, and spent less time reading and writing per day (all P values < 0.05). In the study sample, 23.9% had myopia, 57.6% had hyperopia, and the remaining 18.5% had emmetropia. Cognitive dysfunction was present in 30.4% of persons with myopia, compared with 22.5% with emmetropia and 25.1% with hyperopia.

Table 2 shows the age and sex-adjusted and multivariable-adjusted associations of refractive error with cognitive dysfunction. In the multivariable model after backward stepwise procedure, myopia was associated with cognitive dysfunction (odds ratio [OR] 1.82, 95% confidence interval [CI] 1.05–3.15), compared with emmetropia. Hyperopia was not associated with cognitive dysfunction. Further adjustment for uncorrected refractive errors attenuated the association between myopia and cognitive dysfunction slightly, and the association remained significant (OR 1.78, 95% CI 1.02–3.10). Similarly, further adjustment for best-corrected visual acuity (in logMAR units) of the better eye strengthened associations slightly, and it remained significant (OR 1.86, 95% CI 1.01–3.42). The results were consistent in the supplementary analysis using the alternative definition of myopia as spherical equivalent less than –0.75 (OR 1.68, 95% CI 1.08–2.63).

Table 3 summarizes differences between included and excluded individuals. Excluded individuals were more likely older, female, had higher total and HDL cholesterol, diabetes, and were less likely current smokers. They were also more likely to be less educated, spend fewer hours reading or writing, and have lower income.

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Table 1. Characteristics of Study Participants from the Singapore Malay Eye Study by Cognitive Dysfunction Status

	Cognitive Dysfunction ($n = 267$)			No Cognitive Dysfunction ($n = 765$)			
Characteristic	**No.**	**%**	**Mean (SD)**	**No.**	**%**	**Mean (SD)**	***P* Value**
Age, y			70.5 (5.3)			67.7 (5.3)	<0.001
Female	203	76.0		256	33.5		<0.001
BMI, kg/m^2			25.6 (5.19)			26.1 (4.77)	0.160
Hyperlipidemia	128	48.7		135	51.3		0.669
Total cholesterol, mM			5.74 (1.27)			5.59 (1.21)	0.089
LDL cholesterol			3.64 (1.08)			3.60 (1.05)	0.676
HDL cholesterol			1.39 (0.34)			1.31 (0.32)	0.005
Diabetes	81	30.9		226	30.6		0.920
Glycosylated hemoglobin, %			6.6 (1.6)			6.6 (1.5)	0.774
Hypertension	236	88.4		646	84.6		0.125
History of stroke	13	4.9		25	3.3		0.236
Current smoker	21	7.9		156	20.5		<0.001
Age-related macular degeneration	25	26.9		239	25.7		0.799
Cataract	202	90.2		544	79.5		<0.001
Education level							
No formal education	196	74.0		133	17.5		<0.001
<6 y of education	18	6.8		136	17.9		
6 y education	43	16.2		398	52.3		
High school	6	2.3		79	10.4		
College	2	0.8		15	2.0		
Hours of reading and writing per day							
None	127	49.0		73	9.6		<0.001
0.1–2	123	47.5		601	79.0		
>2–5	8	3.1		59	7.8		
>5	1	0.4		28	3.7		
Income category							
<SG $1000	180	67.9		532	70.5		<0.001
≥SG $1000 to <SG $2000	10	3.8		95	12.6		
≥SG $2000 to <SG $3000	0	0		17	2.3		
≥SG $3000	0	0		3	0.4		
Retired	75	28.3		108	14.3		

P value for difference in characteristics based on a χ^2 test, or independent 2-sample *t*-test. LDL, low-density lipoprotein.

Discussion

Our study found an association between myopia and cognitive dysfunction, relative to emmetropia. This association was independent of age, sex, BMI, income, education, and reading/writing. The association of myopia with cognitive impairment was not related to confounding by cataract. Our results provide preliminary evidence on a novel association between myopia and cognitive dysfunction that should be further studied and need to be replicated in other cohorts.

Reduced vision in older adults has been postulated to affect cognitive function by reducing participation in social, physical, and cognitively stimulating activities that protect against dementia,[24,25] while increasing the risk of depression and anxiety,[26] conditions associated with incident dementia.[27] However, correcting for best-corrected visual acuity and

Table 2. Association of Refractive Error with Cognitive Dysfunction

		Cognitive Dysfunction				
Characteristic	**Persons at Risk**	**% with Cognitive Dysfunction**	**Age-Sex Adjusted Model, OR (95% CI)**	**Multivariable Model 1,† OR (95% CI)**	**Multivariable Model 2,‡ OR (95% CI)**	**Multivariable Model 3,§ OR (95% CI)**
Refractive Error Categories*						
Myopia	247	30.4	1.57 (0.96–2.58)	1.82 (1.05–3.15)	1.78 (1.02–3.10)	1.86 (1.01–3.42)
Hyperopia	594	25.1	1.08 (0.70–1.66)	1.11 (0.68–1.80)	1.09 (0.67–1.78)	0.92 (0.54–1.55)
Emmetropia	191	22.5	1.0	1.0	1.0	1.0

* Myopia, spherical equivalent < –0.5 D; Emmetropia, –0.5 D ≤ spherical equivalent ≤ 0.5 D; Hyperopia, spherical equivalent > 0.5 D.

† Adjusting for age, sex, BMI, education, income, and hours of reading and writing per day.

‡ Adjusting for age, sex, BMI, education, income, hours of reading and writing per day, and uncorrected refractive error. Uncorrected refractive error is defined as at least a two-line difference in logMAR between uncorrected and corrected refractive error in either eye.

§ Adjusts for age, sex, BMI, education, income, hours of reading and writing per day, and logMAR readings of better eye.

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Table 3. Characteristics of Excluded and Included Study Participants from the Singapore Malay Eye Study

Characteristic	Excluded ($n = 477$)			Included ($n = 1032$)			*P* Value
	No.	%	Mean (SD)	No.	%	Mean (SD)	
Age, y			70.0 (5.5)			68.0 (5.4)	<0.001
Female	281	58.9		459	44.5		<0.001
BMI, kg/m^2			25.7 (5.19)			26.0 (4.88)	0.247
Hyperlipidemia	244	51.9		505	49.8		0.449
Total cholesterol, mM			5.77 (1.25)			5.63 (1.23)	0.039
LDL cholesterol			3.61 (1.08)			3.56 (1.05)	0.374
HDL cholesterol			1.41 (0.35)			1.33 (0.32)	<0.001
Diabetes	170	36.3		307	30.7		0.031
Glycosylated hemoglobin, %			6.7 (1.7)			6.6 (1.5)	0.185
Hypertension	425	89.1		882	85.6		0.059
History of stroke	21	4.4		38	3.7		0.499
Current smoker	51	10.7		177	17.2		0.001
Education level							
No formal education	236	49.6		329	32.1		<0.001
<6 y of education	60	12.6		154	15.0		
6 y of education	172	36.1		441	43.0		
High school	7	1.5		85	8.3		
College	1	0.2		17	1.7		
Hours of reading and writing per day							
None	162	34.5		200	19.6		<0.001
0.1–2	286	61.0		724	71.0		
>2–5	17	3.6		67	6.6		
>5	4	0.9		29	2.8		
Income Category							
<SGD $1000	353	74.6		712	69.8		<0.001
≥SG $1000 to <SG $2000	18	4.8		105	10.3		
≥SG $2000 to <SG $3000	2	0.4		17	1.7		
≥SGD $3000	2	0.4		3	0.3		
Retired	98	20.7		183	17.9		

P value for difference in characteristics based on a χ^2 test, or independent 2-sample *t*-test.

uncorrected refractive errors did not change the association between myopia and cognitive dysfunction significantly, suggesting that other mechanisms may be responsible.

What are possible explanations for the association between myopia and cognitive dysfunction? First, it is possible that pathogenic processes in dementia may affect refraction. Some studies have shown that β-amyloid, a key pathogenic feature of cognitive dysfunction, may also accumulate in the lens.[7] Amyloid deposition in the lens can increase lens thickness and curvature, as well as promote lens crystalline aggregation, all of which can increase the refractive index.[8,9] Another possible mechanism is that acetylcholine deficiency, which occurs early in the course of cognitive dysfunction,[28] may reduce parasympathetic input to the ciliary muscle, decreasing the amplitude of accommodation.[29] Suboptimal accommodation during near work leads to hyperopic defocus on the retina, which has been shown to accelerate axial growth.[30] Reduced accommodation in adults has been correlated with myopia progression in some studies, although this was not reported in other studies.[31–33] Second, the association may be due to uncontrolled confounding by other chronic or age-related conditions (i.e., poor general health). Further studies on environmental, pathological genetic, correlates of myopia, and cognitive dysfunction may provide additional insights.

It is noteworthy that education did not significantly modify the association between myopia and cognitive dysfunction in our participants (*P* for interaction = 0.899). Years of education, socioeconomic indicators like income and type of housing, or reading were not significantly different between myopic and nonmyopic individuals in our study (all $P > 0.05$). Most of our older population received elementary education or less (89.5%), and results should be interpreted cautiously when generalizing to more recent birth cohorts, as education and reading, which are frequently associated with myopia in children, are also putative protective factors against cognitive decline in later life.[10]

The strengths of our study include standardized protocols for obtaining refraction and lens opacity measurements. There are some limitations to this study that may have affected the results. First, our study is cross-sectional in nature and the temporality of myopia and cognitive dysfunction is not clear. Second, only ethnic Malay adults were examined in this study and the findings may vary in other ethnic groups. Third, although the AMT is a well-validated screening instrument for cognitive impairment,[34] misclassification may occur, likely biasing OR estimates toward the null hypothesis and inflating their SEs,[35] thereby making actual associations more difficult to detect. Fourth, there may be residual confounding due to factors that we have not controlled for (e.g., depressive symptoms, general well-being, and status of Alzheimer's disease or Parkinson's disease), and categorization of continuous exposure variables (e.g., education level, hours of reading/writing). Fifth, the current sample may not represent the source population due to the high rates of persons with missing cognitive testing (20.2%) and visual impairment (11.4%) data that may introduce bias in this study. Finally, the

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AMT was administered in the participant's preferred language, and a systematic difference is possible between test scores taken in English versus Malay.

In summary, we report a novel finding from population-based data showing an association between myopia and cognitive dysfunction. The specific underlying mechanisms of this association are unknown; however, our results may provide insights into possible common pathways of myopia and cognitive dysfunction.

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