Original Contribution

Relation of Age-related Cataract With Obesity and Obesity Genes in an Asian Population

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Obesity shows an inconsistent association with cataract. Causality has not been established. Polymorphisms at the fat mass- and obesity-associated (*FTO*) locus are associated with obesity and offer an opportunity to examine the obesity-cataract association using a mendelian randomization approach. The authors conducted a population-based study among Singaporean Malay adults (2004–2006) in which nuclear, cortical, and posterior subcapsular (PSC) cataracts were assessed and defined by slit-lamp examination using Lens Opacity Classification System III. Obesity was defined as body mass index (weight (kg)/height (m)^2) ≥30. The study included 3,000 subjects, of whom 1,339 (44.6%) had cataract (848 (28.3%) nuclear, 939 (31.3%) cortical, and 285 (9.5%) PSC). After multivariable adjustment for age, gender, diabetes, hypertension, smoking, and education, obesity was significantly associated with cortical (odds ratio (OR) = 1.31, 95% confidence interval (CI): 1.01, 1.71) and PSC (OR = 1.60, 95% CI: 1.10, 2.32) cataracts but not nuclear cataract. *FTO* single nucleotide polymorphisms known to be associated with obesity in this study population were not associated with cortical or PSC cataract but were associated with nuclear cataract (OR = 1.33, 95% CI: 1.11, 1.58), even in multivariate analyses controlling additionally for body mass index, diabetes, hypertension, and smoking (OR = 1.30, 95% CI: 1.08, 1.55). These results do not support a causal association between obesity and cortical or PSC cataract. The *FTO* gene may be involved in the pathogenesis of nuclear cataract.

cataract; obesity; polymorphism, single nucleotide

Abbreviations: CI, confidence interval; FTO, fat mass- and obesity-associated; LOCS III, Lens Opacity Classification System III; OR, odds ratio; PSC, posterior subcapsular; SD, standard deviation; SNP, single nucleotide polymorphism.

Cataract and obesity are major public health problems worldwide. According to World Health Organization estimates, cataract is the most common cause of blindness, accounting for 47.8% of the 161 million visually disabled people worldwide (1), and various other prevalence surveys have reported the proportion of visual impairment attributable to cataract to be as high as 87% (2, 3). An understanding of risk factors for cataract may result in the identification of strategies for reducing the burden imposed by cataract. Several large epidemiologic studies have evaluated the association between obesity and cataract (4–9). Prospective studies, including the Physicians' Health Study (6, 9), the Nurses' Health Study (7), and the Framingham Eye Study (8), as well as a number of cross-sectional studies (10–13), have demonstrated positive associations between various measures of obesity and cataract. However, not all investigators have reported a consistent association. For example, in the Beaver Dam Eye Study, Klein et al. (14) found no significant association between obesity and incident cataract or cataract extraction, while in 2 other studies Chatterjee et al. (15) and Foster et al. (16) showed that lower body weight was associated with higher cataract prevalence. In addition, there are inconsistencies in the types of cataract associated with obesity, with cortical and posterior subcapsular (PSC) cataracts generally having more consistent and stronger associations (8, 12, 13).

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There is potential for these associations to be the consequence of confounding environmental factors, such as smoking, diet, or socioeconomic position, each of which is associated with obesity and could contribute substantially to the observed relations (17–21). To date, no randomized trials have been conducted to test the causality of these associations, nor do we believe that such trials are practical or feasible. It has been suggested that investigators can exploit the random assignment of genes occurring during gametogenesis as a means of reducing confounding in examining exposure-disease associations. This approach has been described as mendelian randomization. The association between a disease and a genetic polymorphism that serves as a proxy for an environmentally modifiable exposure is not generally susceptible to reverse causation or confounding (22, 23), and this provides a method for assessing the causal nature of some environmental exposures. This approach has been utilized to examine the relation between C-reactive protein and metabolic disease, and the findings suggested that C-reactive protein was not likely to be causal (24, 25). One of the limitations of this approach is that suitable polymorphisms for studying the modifiable exposures of interest may not be available.

Recently, a genome-wide analysis for diabetes susceptibility genes identified a common variant in single nucleotide polymorphisms (SNPs) in intron 1 of the fat mass- and obesity-associated (*FTO*) gene, located on chromosome 16, that predisposes people to childhood and adult obesity (26). We have shown that this polymorphism is both common and associated with obesity among Malays living in Singapore (27). As such, polymorphisms at the *FTO* locus offer an opportunity to examine the association between obesity and cataract using a mendelian randomization approach.

Our aim in this study was to assess the association between obesity and cataract in a Southeast Asian population and to assess the causality of any observed associations by examining the relations between polymorphisms at the *FTO* locus and cataract.

MATERIALS AND METHODS

Study population

This study was conducted among participants in the Singapore Malay Eye Study, a population-based cross-sectional epidemiologic study of 3,280 adults of Malay ethnicity aged 40–80 years residing in Singapore. The methods of the Singapore Malay Eye Study have been described in detail elsewhere (28, 29). An age-stratified random sample comprising 1,400 people from each age decade (40–49, 50–59, 60–69, and 70–80 years) was drawn from a computer-generated list of 15 residential districts provided by the Singapore Ministry of Home Affairs. Of the 5,600 names generated, a door-to-door household visit was made to confirm eligibility. A subject was deemed ineligible if he/she had moved away from the residential address, had not lived there in the past 6 months, was deceased, or was terminally ill. Of the 4,168 eligible persons, 3,280 participated in the Singapore Malay Eye Study between 2004 and 2006, yielding an overall participation rate of 78.7%.

All study procedures were performed in accordance with the tenets of the Declaration of Helsinki as revised in 1989. Written informed consent was obtained from the subjects, and the study protocol was approved by the institutional review board of the Singapore Eye Research Institute.

Study measurements

All subjects underwent a comprehensive physical and ophthalmic assessment, a detailed questionnaire interview, and laboratory measurements (29).

Physical examination. The physical examination included anthropometry and blood pressure measurement. Height was measured in centimeters using a wall-mounted measuring tape, and weight was measured in kilograms using a digital scale (Seca model 782 2321009; Seca Vogel & Halke GmbH, Hamburg, Germany). Height and weight were measured without shoes and with the subject standing. Body mass index was calculated as weight in kilograms divided by height in meters squared (30). A subject was deemed overweight if his or her body mass index was 25–<30 and obese if it was ≥30 (31). Blood pressure was measured with the patient seated after 5 minutes of rest, using an automated sphygmomanometer (Dinamap model Pro Series DP110X-RW, 100V2; GE Medical Systems Information Technologies, Inc., Milwaukee, Wisconsin). Systolic and diastolic blood pressures were taken (32). Two readings were taken 5 minutes apart, with a third reading being taken if the 2 measurements differed by more than 10 mm Hg for systolic pressure or more than 5 mm Hg for diastolic pressure. The mean of the 2 closest readings was then used for the analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or a self-reported history of hypertension.

Cataract assessment. A slit-lamp examination (Haag-Streit model BQ-900; Haag-Streit AG, Koeniz, Switzerland) was performed by study ophthalmologists to assess the anterior segment prior to pupillary dilation. Mydriasis was achieved with tropicamide 1% (2 drops 5 minutes apart) and phenylephrine hydrochloride 2.5% (1 drop) instilled into each eye. Cataracts were then graded by the study ophthalmologists. Lens Opacity Classification System III (LOCS III) standard color photographs were used as the reference for grading, and the grading nomenclature of nuclear color, nuclear opalescence, cortical cataract, and PSC cataract was adopted (33). Grading was based on objective measures of color, density, and area, and each lens was assigned an integer grade with values ranging from 0 to 6 (0–7 in the case of nuclear opalescence).

Any cataract was defined as the presence, in at least 1 eye, of a significant nuclear (nuclear opalescence and nuclear color), cortical, or PSC lens cataract. Significant nuclear cataract was defined by a LOCS III score of >4 for nuclear opalescence or >4 for nuclear color. Significant cortical cataract was defined as a LOCS III score of >2 for cortical cataract, and significant PSC cataract was defined as a LOCS III score of >2 for PSC cataract. If a person had a nongradable lens, the LOCS III score of the fellow eye was used. Definitions of cataracts were based on similar criteria published by us and other research groups using the LOCS III system (16, 34, 35).

Table 1. Characteristics of Study Participants According to Cataract Status, Singapore Malay Eye Study, 2004–2006

Characteristic	Any Cataract ($n = 1,339$)			No Cataract ($n = 1,661$)			P Value[a]
	No.	%	Mean (SD)	No.	%	Mean (SD)	
Age, years			65.8 (8.49)			50.9 (7.48)	<0.001
Male gender	637	47.6		712	48.9		0.472
Weight, kg			64.5 (13.35)			68.2 (13.93)	<0.001
Height, cm			156.7 (9.15)			160.3 (8.88)	<0.001
Body mass index[b]			26.3 (5.12)			26.6 (5.13)	0.166
Overweight[c]	760	56.8		864	59.4		0.270
Diabetes, yes vs. no	416	31.1		206	14.2		<0.001
Hypertension, yes vs. no	1,093	81.6		799	54.9		<0.001
Systolic blood pressure, mm Hg			153.9 (23.98)			140.2 (21.44)	<0.001
Diastolic blood pressure, mm Hg			79.7 (11.18)			80.3 (11.18)	0.125
Total cholesterol, mmol/L			5.7 (1.22)			5.6 (1.09)	0.001
High density lipoprotein cholesterol, mmol/L			1.4 (0.34)			1.3 (0.32)	0.294
Low density lipoprotein cholesterol, mmol/L			3.6 (1.05)			3.5 (0.95)	0.058
Triglycerides, mmol/L			1.7 (1.39)			1.5 (1.24)	0.007
Blood glucose, mmol/L			7.3 (4.02)			6.3 (3.24)	<0.001
Hemoglobin A1c, %			6.7 (1.68)			6.2 (1.36)	<0.001
Serum creatinine, mmol/L			99.7 (70.85)			86.3 (33.87)	<0.001
Alcohol intake, yes vs. no	11	0.8		29	2.0		0.009
Current smoking, yes vs. no	230	17.2		358	24.6		<0.001

Abbreviation: SD, standard deviation.

[a] P value for the difference in characteristics based on a chi-squared test or t test.

[b] Weight (kg)/height (m)^2.

[c] Body mass index 25–<30.

Questionnaire. A detailed interviewer-administered questionnaire was administered to collect relevant sociodemographic and medical information. Data relevant to this study included lifestyle factors (including cigarette smoking history), educational level, eye symptoms and use of glasses, and systemic medical and surgical history.

Laboratory measurements. A 40-mL sample of nonfasting venous blood was collected to determine levels of serum lipids (total cholesterol, high density lipoprotein cholesterol, direct low density lipoprotein cholesterol), hemoglobin A1c, creatinine, and casual glucose (32). All serum biochemistry samples were sent to the reference laboratory of National University Hospital for measurement on the same day. Serum was also collected for DNA extraction and archival at the Singapore Tissue Network, using an automated DNA extraction technique. Extracted DNA samples were aliquoted and stored at −80°C.

Genotyping. Ten SNPs at the *FTO* locus were selected for examination in this study. All were within intron 1 of the gene and had been shown to be associated with obesity in previous reports (26, 36–41). Genotyping was performed with the Sequenom iPLEX Gold system, as per the manufacturer's protocol (Sequenom, Inc., San Diego, California). Briefly, multiplex SNP assays were designed using Sequenom's

MassARRAY Assay Design software for the 10 chosen SNPs, followed by polymerase chain reaction amplification of the DNA region of interest, cleanup with shrimp alkaline phosphatase, and primer extension. Primer extension products were spotted onto a Sequenom SpectroCHIP and analyzed by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. All assays gave a genotype call rate above 99%. One polymorphism, rs9930506, was excluded from this study because it failed the assay design. All SNPs included in this study showed a high degree of linkage disequilibrium ($R^2 > 0.8$) in this population, consistent with previous reports (27, 36). The SNP rs9939609 was chosen for presentation in this manuscript, since it has been shown to have the strongest association with obesity in both Caucasian populations (26, 42) and non-Caucasian multiethnic populations (43, 44). The associations with other SNPs studied were similar to those of rs9939609, and these data are presented in the Appendix Table.

Statistical analysis

Hardy-Weinberg equilibrium for each polymorphism was tested by χ^2 test. Of the 3,280 participants, 166 did not give consent for DNA collection, 112 had insufficient DNA for

genetic analysis, and 2 had data errors. Thus, a total of 3,000 participants were genotyped. Pairwise linkage disequilibrium measures between polymorphisms and expectation-maximization algorithm-based haplotype associations were computed using Haploview (44). All other statistical analyses were performed using R 2.5.1 (R System for Statistical Computing; Comprehensive R Archive Network (http://www.r-project.org)). We applied logistic regression analysis to evaluate the association between each SNP and the presence of any cataract under an additive model of inheritance, since the association between SNPs at the *FTO* locus and obesity best fitted an additive model. Cataract was likewise assessed as a categorical variable for the presence of any cataract, as well as the presence of any cataract in each of the 3 regions (nuclear, cortical, or PSC). In further analyses, we controlled for potential confounders such as age, gender, body mass index, diabetes mellitus, hypertension, smoking, and educational level.

RESULTS

The clinical characteristics of the study population are summarized in Table 1. Of the 3,000 subjects included in the study, 1,339 had any cataract. Significant differences were found in a number of parameters between subjects with no cataract and the group with any cataract. Subjects with any cataract were older (mean age = 65.8 years (standard deviation (SD), 8.49) vs. 50.9 years (SD, 7.48); $P < 0.001$) and had a lower body weight (64.5 kg (SD, 13.35) vs. 68.2 kg (SD, 13.93); $P < 0.001$). They were also more likely to have diabetes, hypertension, and high levels of total cholesterol and triglycerides. Subjects with cataracts were less likely to be smokers (17.2% vs. 24.6%; $P < 0.001$).

The results of an analysis of the association between obesity and cataract in our study population are shown in Table 2. After adjustment for age and gender, obesity was associated with increased risks of both cortical and PSC cataract (odds ratio (OR) = 1.40 (95% confidence interval (CI): 1.08, 1.80) and OR = 1.67 (95% CI: 1.15, 2.40), respectively). With further adjustments for diabetes, hypertension, smoking, and educational level, these associations persisted (OR = 1.31 (95% CI: 1.01, 1.71) and OR = 1.60 (95% CI: 1.10, 2.32), respectively).

The 9 SNPs genotyped showed a high degree of linkage disequilibrium ($R^2 > 0.8$). Associations between all 9 SNPs and cataract were similar (see Appendix Table). For this reason, only the associations with rs9939609, the index SNP identified in the initial studies (26) and the SNP which showed the strongest association with obesity, are shown (Table 3). A high call rate was obtained for rs9939609, with the genotype being reliably derived by the assay in 2,985 (99.5%) samples. The minor allele frequency was 0.30. There was no deviation from Hardy-Weinberg equilibrium ($P = 0.99$). In linear regression models, rs9939609 showed a highly significant positive association with body mass index under an additive model of inheritance, with an effect of 0.64 units (95% CI: 0.35, 0.91; $P < 0.001$) per copy of the allele present (27). Thus, a person who is homozygous for the minor allele has a body mass index 1.28 times higher, on average, than someone who is homozygous for the major allele.

Table 2. Association Between Obesity and Cataract Outcomes, Singapore Malay Eye Study, 2004–2006

	No. at Risk	Any Cataract				Nuclear Cataract				Cortical Cataract				Posterior Subcapsular Cataract			
		No. of Cases	%	OR	95% CI	No. of Cases	%	OR	95% CI	No. of Cases	%	OR	95% CI	No. of Cases	%	OR	95% CI
Age- and gender-adjusted model																	
BMI[a]																	
Normal	1,155	565	48.9	1.0	Referent	386	33.8	1.0	Referent	384	33.7	1.0	Referent	112	9.9	1.0	Referent
Overweight[b]	1,032	486	47.1	1.06	0.83, 1.34	294	28.8	0.92	0.71, 1.19	342	33.4	1.15	0.93, 1.42	106	10.5	1.35	1.00, 1.84
Obese[b]	592	274	46.3	1.17	0.88, 1.56	158	26.9	0.90	0.66, 1.24	203	34.8	1.40	1.08, 1.80	65	11.2	1.67	1.15, 2.40
P value					0.55				0.75				0.036				0.017
Multivariable model[c]																	
BMI																	
Normal	1,155	565	48.9	1.0	Referent	386	33.8	1.0	Referent	384	33.7	1.0	Referent	112	9.9	1.0	Referent
Overweight	1,032	486	47.1	1.03	0.81, 1.32	294	28.8	0.90	0.69, 1.16	342	33.4	1.13	0.91, 1.40	106	10.5	1.33	0.98, 1.82
Obese	592	274	46.3	1.09	0.81, 1.47	158	26.9	0.87	0.63, 1.20	203	34.8	1.31	1.01, 1.71	65	11.2	1.60	1.10, 2.32
P value					0.84				0.61				0.13				0.037

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.
[a] Weight (kg)/height (m)^2.
[b] A person was defined as overweight if BMI was 25–<30 and obese if BMI was ≥30.
[c] Results were adjusted for age, gender, diabetes, hypertension, smoking, and education.

Table 3. Association Between the Minor Allele of the *FTO* Single Nucleotide Polymorphism rs9939609 and Cataract Outcomes (Additive Model), Singapore Malay Eye Study, 2004–2006

	Any Cataract (n = 1,339)		Nuclear Cataract (n = 848)		Cortical Cataract (n = 939)		Posterior Subcapsular Cataract (n = 285)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age- and gender-adjusted model	1.17	1.00, 1.37	1.33	1.11, 1.58	1.00	0.87, 1.16	0.86	0.70, 1.07
P value		0.056		0.002		0.954		0.175
Multivariable model[a]	1.14	0.97, 1.34	1.30	1.08, 1.55	0.96	0.83, 1.11	0.80	0.64, 0.98
P value		0.13		0.004		0.57		0.035

Abbreviations: CI, confidence interval; FTO, fat mass- and obesity-associated; OR, odds ratio.
[a] Results were adjusted for age, gender, body mass index, diabetes, hypertension, and smoking.

Under an additive model of inheritance, each copy of the minor allele for rs9939609 (the same allele associated with elevated body mass index) was associated with a 1.33-fold greater risk of having nuclear cataract after adjustment for age and gender. In multivariate analyses controlling additionally for body mass index, diabetes, hypertension, and smoking, the association between rs9939609 and nuclear cataract (OR = 1.30, 95% CI: 1.08, 1.55; *P* = 0.004) was maintained. There was no association with any cataract or with cortical or PSC cataract, although there was a significant protective association with PSC cataract after multivariate adjustment (Table 3).

A further logistic regression analysis, stratified according to obesity or overweight status in lieu of body mass index and controlling similarly for age, gender, diabetes, hypertension, and smoking, showed similar associations between rs9939609 and the presence of any cataract or nuclear cataract (Table 4). Analysis of the other 8 SNPs produced similar findings.

DISCUSSION

Our study, carried out in a large Asian population, shows that obesity is associated with increased risk of cortical and PSC cataracts but not nuclear cataract. These findings are

Table 4. Association Between the *FTO* Single Nucleotide Polymorphism rs9939609 and Cataract Outcomes, by Obesity and Diabetes Status, Singapore Malay Eye Study, 2004–2006

Characteristic	rs9939609 Genotype[a]	Any Cataract						Nuclear Cataract					
		No. at Risk	No. of Cases	%	Multivariable OR[b]	95% CI	P for Interaction	No. at Risk	No. of Cases	%	Multivariable OR[b]	95% CI	P for Interaction
All subjects	2	241	124	51.5	1.67	1.16, 2.42		238	78	32.8	1.67	1.11, 2.50	
	1/0	2,553	1,215	47.6	1.0			2,525	770	30.5	1.0		
P value					0.006						0.013		
Overweight[c]													
Yes	2	174	88	50.6	1.75	1.15, 2.66	0.817	172	50	29.1	1.51	0.94, 2.41	0.243
	1/0	1,450	672	46.3	1.0			1,435	402	28.0	1.0		
P value					0.010						0.088		
No	2	66	36	54.5	1.43	0.65, 3.13		65	28	43.1	2.09	0.92, 4.73	
	1/0	1,089	529	48.6	1.0			1,077	358	33.2	1.0		
P value					0.373						0.078		
Diabetes													
Yes	2	74	52	70.3	2.26	1.14, 4.46	0.633	72	38	52.8	2.42	1.24, 4.73	0.233
	1/0	548	364	66.4	1.0			536	248	46.3	1.0		
P value					0.019						0.010		
No	2	167	72	43.1	1.49	0.95, 2.33		166	40	24.1	1.36	0.81, 2.28	
	1/0	2,005	851	42.4	1.0			1,989	522	26.2	1.0		
P value					0.083						0.252		

Abbreviations: CI, confidence interval; FTO, fat mass- and obesity-associated; OR, odds ratio.
[a] Genotype represents the number of risk/minor alleles (0, 1, or 2).
[b] Results were adjusted for age, gender, diabetes, hypertension, and smoking.
[c] Body mass index 25–<30.

consistent with data from some existing studies (8, 12, 13). Leske et al. (45) have even reported that nuclear cataracts may be associated with leaner body mass rather than obesity, which we also observed, although the association did not reach statistical significance. However, the rare allele for the SNP rs9939609, which is associated with greater obesity in our population (27) and many other populations (26, 40, 43, 44, 46, 47), did not show any association with either cortical or PSC cataract. This does not support a causal relation between obesity and cortical or PSC cataract.

The finding that the same genetic variants at the *FTO* locus are associated with nuclear cataract was unexpected and novel, because obesity per se was not associated with nuclear cataract. While the heritability of age-related cataract has been strongly suggested from a number of genetic epidemiologic studies (48, 49), efforts at identifying the major genetic factor contributing to age-related cataracts have succeeded only in identifying a number of candidate genes belonging to protective, metabolic, or regulatory pathways that are up- or down-regulated in cataract formation (50–52). We believe that the *FTO* locus may represent a new susceptibility locus for nuclear cataracts.

We believe our data further support the hypothesis that the molecular mechanisms involved in the pathogenesis of nuclear, cortical, and PSC cataracts differ. PSC cataracts are associated with abnormalities in the lens germinal epithelium (53) that lead to abnormal proliferation and migration of lens epithelial cells. While oxidative stress contributes to the formation of both age-related nuclear cataracts and cortical cataracts (54), the manner in which it does so differs. The lens cortex, being situated in the outer zone of the lens, is perhaps more susceptible to exogenous oxidative insults transmitted through the aqueous humor than the deeply situated nucleus. The cortex is also metabolically active, while the nucleus is metabolically inactive and dependent on the transport of antioxidants like glutathione from the cortex. Truscott and Augusteyn have shown that large decreases in nuclear glutathione concentration can occur despite normal levels in the cortex in cataractous lenses (55), which has led some authors to propose the concept of an internal lens barrier to diffusion of glutathione that contributes to nuclear cataract (56, 57). The nature of this lens barrier is not clearly understood, but altered membrane lipids are likely to contribute (54, 58). Furthermore, Truscott and Elderfield (59) and Streete et al. (60) have shown that abnormalities in protein biochemistry in cataractous lenses are associated with generalized systemic alterations of amino acid transport, and, analogously, it is conceivable that systemic differences in lipid trafficking may contribute to the development of the internal lens barrier and subsequent nuclear cataract formation. Although the function of the *FTO* gene product is currently unknown, Sanchez-Pulido and Andrade-Navarro (61) performed computational characterization of the *FTO* gene and concluded that it is a member of the nonheme dioxygenase (Fe(II)- and 2-oxoglutarate-dependent dioxygenases) superfamily. Gerken et al. (62) further characterized the function of murine *FTO* as catalyzing the Fe(II)- and 2-oxoglutarate-dependent demethylation of 3-methylthymine in single-stranded DNA, and an in vitro characterization of human *FTO* by Jia et al. (63) has clari-

fied its primary role as an RNA demethylase that may have a gene regulatory function at the RNA level. Based on current data, a role for the *FTO* gene product as a cellular metabolic sensor has been proposed (61). One possible explanation for our findings is that genetic variants at the *FTO* locus are associated with an altered lipid metabolic pathway that in turn has differential effects on the various zones of the lens.

The strengths of our study include a large population-based sample and the availability of standardized clinical and laboratory measures. Potential limitations include nonparticipation bias and subjectivity in cataract assessment and grading. The latter, however, is a nondifferential measurement error, since the examiners had no knowledge of the genotype; the effect, if any, would have been to bias the associations towards the null hypothesis and thus not alter the interpretation of our findings. The relatively small number of subjects with PSC cataract also limited the study's power to detect an association. The racial homogeneity of our study population also limits the generalizability of our findings, since phenotypic expression of *FTO* variants is known to vary with ethnicity (38, 46). In addition, body mass index was measured at only a single time point, which may not adequately represent a person's lifetime exposure to obesity. This could have resulted in underadjustment for obesity in our models.

In conclusion, we have demonstrated that obesity is associated with cataract in an Asian population and that this association is primarily with cortical and PSC cataract, not with nuclear cataract. No association was observed between polymorphisms at the *FTO* locus and cortical or PSC cataract, which does not support a causal relation between obesity and cortical or PSC cataract. An unexpected association between these polymorphisms and nuclear cataract was also observed. Although this suggests that *FTO* may be involved in the pathogenesis of age-related nuclear cataract, the association is unexplained and requires further replication and additional study.

ACKNOWLEDGMENTS

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Appendix Table. Associations Between Individual *FTO* Single Nucleotide Polymorphisms and Cataract Outcomes (Additive Model), Singapore Malay Eye Study, 2004–2006[a]

Single Nucleotide Polymorphism	Any Cataract (*n* = 1,339)		Nuclear Cataract (*n* = 848)		Cortical Cataract (*n* = 939)		Posterior Subcapsular Cataract (*n* = 285)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
rs9939609	1.17	1.00, 1.37	1.33	1.11, 1.58	1.00	0.87, 1.16	0.86	0.70, 1.07
rs9939973	1.18	1.01, 1.38	1.30	1.10, 1.53	1.05	0.92, 1.21	0.86	0.70, 1.05
rs9940128	1.18	1.01, 1.38	1.29	1.09, 1.53	1.06	0.92, 1.21	0.85	0.70, 1.05
rs1421085	1.19	1.01, 1.39	1.32	1.11, 1.58	1.02	0.89, 1.18	0.86	0.70, 1.07
rs1121980	1.15	0.99, 1.34	1.28	1.08, 1.51	1.03	0.90, 1.19	0.86	0.70, 1.05
rs7193144	1.16	0.99, 1.36	1.31	1.10, 1.55	1.00	0.87, 1.15	0.87	0.71, 1.07
rs17817449	1.17	1.00, 1.38	1.32	1.11, 1.58	1.01	0.88, 1.17	0.86	0.70, 1.06
rs8050136	1.18	1.00, 1.38	1.32	1.11, 1.58	1.01	0.88, 1.17	0.86	0.69, 1.06
rs9926289	1.17	1.00, 1.37	1.33	1.12, 1.59	1.01	0.88, 1.17	0.87	0.70, 1.07

Abbreviations: CI, confidence interval; FTO, fat mass- and obesity-associated; OR, odds ratio; rs, reference SNP [single nucleotide polymorphism].

[a] Results were adjusted for age and gender.