Association between parental myopia and the risk of myopia in a child

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Abstract. The association between parental myopia and a child's risk of developing the condition is not well understood. Therefore, the present study conducted a meta-analysis of the results of observational studies in order to investigate the association between myopia in parents and their child's risk of developing the condition. The current study systematically examined the databases MEDLINE, Embase and Ovid for relevant studies. Two reviewers independently evaluated the data and extracted the odds ratios (ORs) and 95% confidence intervals (CIs) from the suitable studies. Heterogeneity, publication bias and subgroup analyses were performed. The present meta-analysis included 31,677 participants from 16 studies with 8,393 cases of myopia (six prospective cohort, eight cross-sectional and two case-control studies). The OR of giving birth to a child with myopia, according to the prospective cohort, cross-sectional and case-control studies, was 1.53 (95% CI, 1.21-1.85), 1.96 (95% CI, 1.53-2.39), and 2.13 (95% CI, 1.79-2.46), respectively, when one parent had myopia, and 2.10 (95% CI, 1.42-2.77), 2.96 (95% CI, 2.21-3.71), and 2.13 (95% CI, 1.79-2.46), respectively, when two parents had myopia. The current study identified a significant positive association between parental myopia and a child's risk of developing myopia. Children of two parents with myopia had a higher risk of developing myopia compared to those with one myopic parent.

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Introduction

Myopia is a global health problem that has social, educational and economic consequences, and significantly affects the quality of life of sufferers (1). There is growing evidence to suggest that the prevalence of myopia is increasing; it is one of the five ocular conditions that are considered an immediate priority by the World Health Organization's Global Initiative for the Elimination of Avoidable Blindness (2). There is considerable variation in the prevalence rate of myopia worldwide. Currently, ~1/3 of the world's population is affected (3,4), and in certain populations in East Asia, the incidence rate of myopia is >80% (5-8). Although there are numerous methods of improving the blurred vision associated with myopia, including wearing corrective lenses or refractive surgery, possible interventions for the pathogenesis of myopia have been intensively studied. Several studies have revealed that a parental history of myopia may be linked to the prevalence of the disorder; however, it is not yet understood whether parental myopia denotes a common family environment or a genetic susceptibility (9-11).

A number of epidemiological studies have demonstrated a positive association between the prevalence of myopia in parents and a child's risk of developing myopia (12-14). However, there are large inconsistencies in the odds ratios (ORs) among these studies (ranging from 1.48 to 7.90). Furthermore, other studies have identified no statistically significant association between parental myopia and a child's risk of developing myopia (15-17). These contrasting conclusions may be due to differences in the study designs. The association between parental myopia and a child's risk of developing myopia has not yet, to the best of our knowledge, been investigated through meta-analysis. Therefore, the present study conducted a meta-analysis, by extracting data from observational studies with various designs, to quantitatively investigate the association between parental myopia and a child's risk of developing myopia.

Materials and methods

Study outline. The current study systematically reviewed potentially eligible literature for a meta-analysis of prospective cohort, cross-sectional and case-control studies in accordance with the Meta-analysis of Observational Studies

in Epidemiology (MOOSE) guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (18,19).

Search strategy. The MEDLINE (articles from 1966 to June 1, 2013), Embase (articles from 1980 to June 1, 2013), and Ovid (articles from 1950 to June 1, 2013) databases were searched for prospective cohort, cross-sectional and case-control studies that did not have access restrictions. All relevant studies using Medical Subject Headings (MeSH) or free text words were selected. The MeSH search strategies were followed and the search terms for exposure (parent, parental, family, history), and outcomes (myopia, myopic, short-sight, short sight, near-sight, near sight, refractive errors) were combined. Furthermore, a number of potential studies were identified electronically by searching the reference lists of the relevant publications. These publications were scrutinized in an effort to identify additional relevant studies.

Selection criteria. The reviewers independently evaluated potential published studies that quantitatively estimated the association between parental myopia and a child's risk of developing myopia. The titles of the studies were first evaluated to ascertain the possibility of the study fitting the selection criteria of the meta-analysis. The abstracts, as well as the methods and results, of studies that were deemed potentially relevant were subsequently reviewed. Those studies over which there was uncertainty as to whether they fulfilled the selection criteria were also reviewed. Any discrepancies between the reviewers were resolved through arbitration, and any differences were settled by consensus. Studies were included in the meta-analysis if they fulfilled the following criteria: i) children, adolescents or youth were included as participants; ii) the exposure of interest was parents with myopia; iii) the outcome of interest was myopia amongst children (prevalent or incident) and; iv) risk estimates, including relative risks (RRs), ORs, hazard ratios (HRs), or other measures that it was possible to transform into ORs with 95% confidence intervals (CIs), were reported. Studies that did not meet the inclusion criteria were excluded during the initial review phase.

Data extraction and quality assessment. The reviewers independently extracted all data using a standardized data collection form. Any inconsistencies were resolved through discussion and by consulting the original articles. The following data were collected from each study: first author's surname, publication year, country, recruitment date, size of the study population, gender and age of the participants, number of cases, measure and range of exposure, and risk estimates with corresponding CIs of a child's risk of developing myopia. ORs and 95% CIs that reflected the degree of control for potential confounders were extracted for use in the main analyses. A third reviewer resolved any disagreement in the abstracted data.

Statistical analysis. The OR was used to assess associations across studies. RRs and HRs were transformed into ORs using a previously described method (20). The OR was pooled to summarize the associations between one or two parents with myopia and a child's risk of developing the condition.

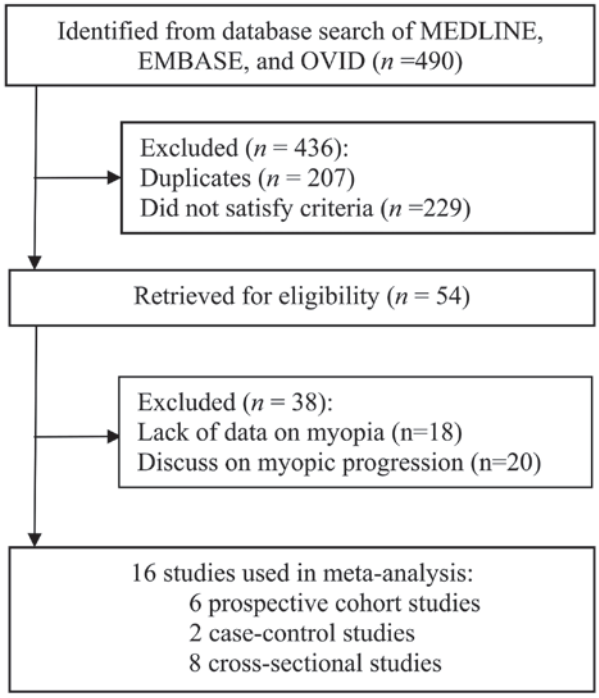

Figure 1. Flowchart of the study selection process.

Pooled estimations and complete analyses across studies were obtained using random-effects models throughout the meta-analysis (21). The heterogeneity of the studies was assessed using Cochran's Q test and the I^2 statistic (22). As suggested by Higgins and Thompson, I^2 values of 25, 50 and 75% were considered to indicate low, moderate and high heterogeneity, respectively (23). Subgroup analyses were conducted to assess the potential association between a child's risk of developing myopia and relevant study characteristics (including participants' age, geographical location, follow-up time, recruitment date and the study design) as possible sources of heterogeneity. A funnel plot of the overall ORs was generated and this produced a standard error (ER) which was used to assess publication bias using Egger's and Begg's regression tests. The 'trim and fill' procedure was also performed to ascertain the possible effect of publication bias in the meta-analysis. This method considered the possibility of hypothetical 'missing' studies and imputed their RRs, thus obtaining a pooled RR that combined the hypothetical missing studies with the actual studies used (24,25). Stata 10 (StataCorp, College Station, TX, USA) was used to carry out all the analyses. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Final study inclusions. Fig. 1 shows the detailed procedure that was employed to search for the literature included in the current meta-analysis. Following the evaluation of titles and abstracts, 54 manuscripts were identified that fulfilled the selection criteria of the present study. The full texts of these studies were reviewed for eligibility. Following this review, a number of manuscripts were excluded due to information, including outcome, the exposure of interest or essential data,

being omitted. A total of 16 studies were eligible for final inclusion (12-17,26-34). Of these, six were prospective cohort (12,13,15,17,31,32), eight were cross-sectional (14,16,26-30,35) and two were case-control studies (33,34).

Characteristics and quality of the study cohorts. Table I shows the characteristics of the included studies. The present meta-analysis included 16 studies with 8,393 cases of myopia. The selected studies were from four continents (seven from Asia (14,16,26,28,32,34,35), four from Europe (17,29,31,33), three from the United States (12,13,30) and two from Australia (15,27). All of the studies recruited male and female participants aged ≤31 years. The majority of studies used questionnaires to ascertain the parents' history of myopia and to assess whether parents wore spectacles or contact lenses at the time of the study. Seven of the studies identified the participants' myopia as a spherical equivalent refraction (SER) ≤-0.5 diopters (D) (14-16,27,28,33,35) and two studies identified the participants' myopia as a SER ≤-0.75 D (26,32). Three of the studies reported the participants' myopia as a SER ≤-0.75 D in the horizontal and vertical meridians following cycloplegic autorefraction (12,13,30). The participants' myopia in another four studies was identified as SER ≤-1.5 D (17), a visual acuity ≥6/9 following correction with a concave lens >0.5 D (34), a SER between -0.75 and -2.99 D (31), and self-reported wearing of 'minus' glasses (29).

Main analyses. A total of 16 studies with 31,677 participants and 8,393 cases of myopia were included in the present analysis. The pooled ORs for each study and for the studies that combined data for 'having parents with myopia' vs. 'no parents with myopia' are shown in Fig. 2. There was a statistically significant positive association between myopia in one or two parents and a child's risk of developing myopia. The ORs and 95% CIs in the prospective cohort, cross-sectional and case-control studies were 1.53 (95% CI, 1.21-1.85), 1.96 (95% CI, 1.53-2.39), and 2.13 (95% CI, 1.79-2.46), respectively, for myopia in one parent and 2.10 (95% CI, 1.42-2.77), 2.96 (95% CI, 2.21-3.71), and 2.13 (95% CI, 1.79-2.46), respectively, for myopia in two parents. No heterogeneity was observed in the case-control studies with myopia in one or two parents ($P=0.39$, $I^2=0\%$).

Publication bias. Visual inspection of the funnel plot revealed a certain level of asymmetry. The Begg's test (P=0.18 and P=1.00 for included cohort and cross-sectional studies, respectively) and Egger's test (P=0.05 and P=0.46 for included cohort and cross-sectional studies, respectively) did not suggest any evidence for publication bias in the analysis of participants with one parent with myopia. However, Egger's test implied a certain level of publication bias in studies that investigated the association between a child's risk of myopia and myopia in two parents (P=0.03 and P=0.04 for included cohort and cross-sectional studies, respectively) whereas Begg's test did not (P=0.05 and P=0.22 for included cohort and cross-sectional studies, respectively). The 'trim and fill' method identified the existence of possible missing studies in the analysis of participants with myopia in one parent (two and three missing cohort and cross-sectional studies, respectively) and with myopia in two parents (three and four missing cohort and cross-sectional studies, respectively). However, the filled studies did not influence the results (for myopia in one parent OR, 1.44; 95% CI, 1.03-1.84 in cohort studies; OR, 1.85; 95% CI, 1.47-2.23 in cross-sectional studies; for myopia in two parents: OR, 1.79; 95% CI, 1.09-2.48 in cohort studies; OR, 2.56; 95% CI, 1.78-3.35 in cross-sectional studies).

Subgroup and sensitivity analyses. With respect to the sensitivity analysis, Table II shows the results of subgroup analyses stratified according to the study characteristics. For the prospective cohort studies, age, geographical location, recruitment date or years of follow-up did not significantly influence the association between myopia in one parent and a child's risk of developing myopia. Neither age nor years of follow-up influenced the association between myopia in two parents and a child's risk of developing the condition. Geographical location and recruitment date were identified to be possible sources of heterogeneity (P<0.01 and P=0.03, respectively) in the studies of myopia in two parents.

The present study examined age and geographical location as possible sources of heterogeneity in the cross-sectional studies. Age and geographical location were observed as sources of heterogeneity (both P<0.01) in studies with myopia in one parent; however there was no evidence that age or geographical location were a source of heterogeneity in studies with myopia in two parents.

Discussion

The current study, which included 31,677 participants and 8,393 cases of myopia, revealed that parental myopia has a significant positive association with a child's risk of developing myopia. Children of two parents with myopia have a higher risk of developing myopia than those who have one parent with myopia.

The underlying mechanisms responsible for this association may be consistent with genetic and environmental factors, or with gene-environment interactions (27,36-41). Zadnik *et al* reported that the eyes of children who had two parents with myopia had longer axial lengths and a smaller hyperopic refractive error than the eyes of children who had one or no parents with myopia (11). A cross-sectional sample from the Orinda Longitudinal Study of Myopia in 716 children, aged from 6 to 14 years, confirmed these results (30). These studies suggest that the size of pre-myopic eyes may be influenced by parental myopia (42), and that a higher number of myopic parents is associated with an increase in the axial length of eyes in childhood (11,43).

A number of previous studies have extensively examined the impact of genetic effects on myopia in humans (44-46). The analysis of genes involved in the scleral extracellular matrix (ECM) is a common feature of studies on syndromic high myopia (47). A meta-analysis that investigated the genetic variants of the high myopia present in the Han Chinese population confirmed that four single nucleotide polymorphisms (SNPs) have genome-wide significance. Of these SNPs, rs2730260 is located on the VIPR2 gene, which is positioned in the MYP4 locus, whilst the other three SNPs (rs7839488, rs4395927, and rs4455882) are in the same linkage disequilibrium block, which is located on the SNTB1 gene. The VIPR2 and SNTB1

Table I. Characteristics of the studies included in the meta-analysis of published studies on a child's risk of developing myopia with myopic parents.

Study (Ref.)	Country	Design	Study name	Gender and age (years)	Recruitment date (years of follow-up)	No. of cases (study size)	Definition of myopia	Adjustments
French *et al* 2013 (15)	Australia	Cohort	Sydney Adolescent Vascular and Eye Study (SAVES)	Male/female (9.5)	2003-2005 (6.1)	335 (2,059)	SER ≤-0.5 D	Age and gender
Xiang *et al* 2012 (14)	China	Cross-sectional	Guangzhou refractive error study in children (RESC)	Male/female (5-15)	2002 (-)	3,421 (4,364)	SER ≤-0.5 D	-
Wu *et al* 2010 (26)	Taiwan	Cross-sectional	-	Male/female (7-12)	2007 (-)	45 (145)	SER ≤-0.75 D	-
Low *et al* 2010 (16)	Singapore	Cross-sectional	STrabismus, Amblyopia and Refractive error Singaporean children (STARS) study	Male/female (0.5-6)	2006 and 2008 (-)	301 (3,009)	SER ≤-0.5 D	Family clusters, age gender, height, time spent outdoors, and words or pictures read
Jones-Jordan *et al* 2010 (13)	United States	Cohort	Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE)	Male/female (6)	1989-2005 (5.32)	334 (1,854)	SER ≤-0.75 D in both the horizontal and vertical meridians.	Gender, site and ethnicity
Konstantopoulos *et al* 2008 (33)	Greece	Case-control	-	Male/female (17-31)	2002-2003 (-)	99 (200)	SER ≤-0.5 D	-
Williams *et al* 2008 (17)	UK	Cohort	Avon Longitudinal Study of Parents and Children (ALSPAC)	Male/female (7-10)	1991 (7)	102 (6,871)	SER ≤-1.5 D	Gender, mother's partner's education, and ethnicity
Ip *et al* 2007 (27)	Australia	Cross-sectional	Sydney Myopia Study (SMS)	Male/female (11.1-14.4)	-	220 (2,353)	SER ≤-0.5 D	Age, gender, near work, time spent outdoors, and ethnicity
Jones *et al* 2007 (12)	United States	Cohort	Orinda Longitudinal Study of Myopia	Male/female (8-9)	1989 (12)	111 (514)	SER ≤-0.75 D in the horizontal and vertical meridians.	Hours spent doing sports/being outdoors and reading
Onal *et al* 2007 (31)	Turkey	Cohort	-	Male/female (18-26)	2003 (1)	68 (207)	SER between -0.75 and -2.99 D	-

Table I. Continued.

Study (Ref.)	Country	Design	Study name	Gender and age (years)	Recruitment date (years of follow-up)	No. of cases (study size)	Definition of myopia	Adjustments
Saw *et al* 2006 (32)	Singapore	Cohort	Singapore Cohort Study Of the Risk Factors for Myopia (SCORM)	Male/female (7-9)	1999 (3)	454 (994)	SER ≤-0.75 D	Age, gender, school, parental income, books read per week, and IQ
Khader *et al* 2006 (28)	Jordan	Cross-sectional		Male/female (12-17)	-	313 (1,777)	SER ≤-0.5 D	-
Khandekar *et al* 2005 (34)	Oman	Case-control	-	Male/female (16-17)	2002-2003 (-)	1440 (2,853)	Vision 6/9 or more following correction with concave lens of >0.5 D	-
Vannas *et al* 2003 (29)	Finland	Cross-sectional	-	Male/female (19.2)	1999-2000 (-)	782 (3,524)	Self-reported wearing of 'minus' glasses	Conscript's education, eye color, BMI, sunglasses wearing, region, myopic siblings, parents' education, unweighted near-work and weighted near-work
Saw *et al* 2002 (35)	Singapore and China	Cross-sectional	-	Male/female (7-9)	1999-2000 (-)	299 (957)	SER ≤-0.5D	Books read per week, age, night-light use prior to 2 years of age and country
Mutti *et al* 2002 (30)	United States	Cross-sectional	Orinda Longitudinal Study of Myopia	Male/female (13-14)	1991 (5)	67 (366)	SER ≤-0.75D in the horizontal and vertical meridians	Diopter-hours per week, sports, reading, local ITBS percentile score and ITBS total language local percentile score

SER, spherical equivalent refraction; D, diopter; IQ, intelligence quotient; BMI, body mass index; PEM, protein-energy malnutrition; ITBS, Iowa Tests of Basic Skills.

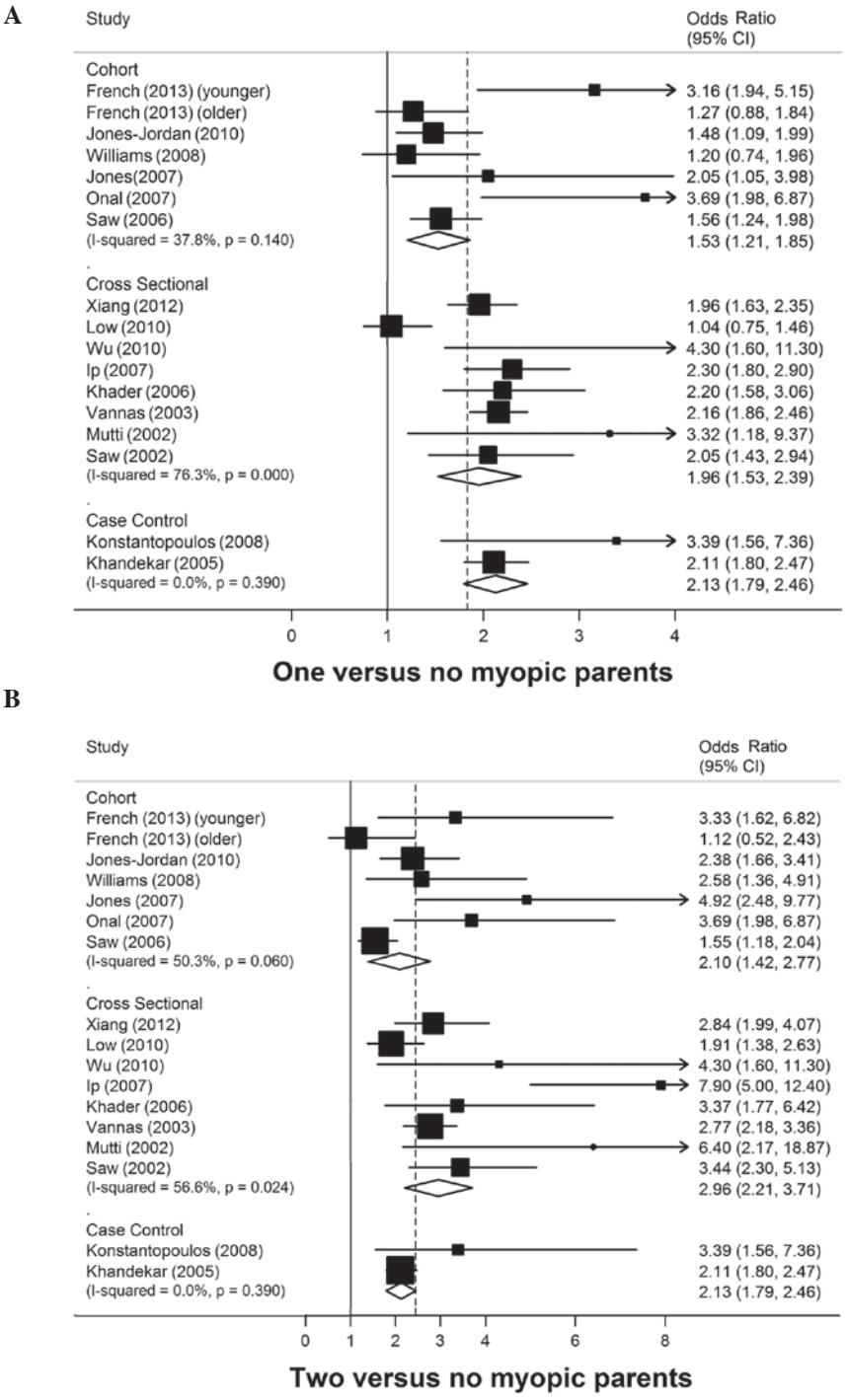

Figure 2. Association between a child's risk of developing myopia when having (A) one or (B) two myopic parents.

genes are expressed in the retina and in the retinal pigment epithelium. The authors of the study therefore suggested that variants of the VIPR2 and SNTB1 genes increase susceptibility to high myopia in the Han Chinese population (48).

A large number of chromosomal localizations have been reported (MYP1-MYP17) for cases of non-syndromic high myopia; however, only a few specific genes have been identified. MYP16 is an exception since mutations in the cadherin-associated protein, situated on this gene, have been identified and replicated (47,49). Although there are several issues with replication, Wojciechowski (44) demonstrated that a number of the reported mutations form a coherent nexus of linked structural and metabolic constituents in the scleral ECM. A recent genome-wide meta-analysis, which included 27 studies with participants of European ancestry and five Asian cohorts, identified 16 new loci for refractive error in individuals with European ancestry. Eight of these loci are shared with individuals of Asian descent. The new loci include candidate genes with functions in neurotransmission (GRIA4), ion transport (KCNQ5), retinoic acid metabolism (RDH5), ECM remodeling (LAMA2 and BMP2), and eye development (SIX6 and PRSS56) (50). Genes associated with a hereditary susceptibility for myopia may explain the results obtained in the present meta-analysis.

Table II. Subgroup analysis for myopia (one or two parents with myopia vs. no parents with myopia).

Subgroups	No. of studies	Heterogeneity within subgroup in participants with one myopic parent			P-value for heterogeneity between subgroups	Heterogeneity within subgroup in participants with two myopic parents			P-value for heterogeneity between subgroups
		OR (95% CI)	I^2 (%)	P-value for heterogeneity		OR (95% CI)	I^2 (%)	P-value for heterogeneity	
Cohort									
Age (years)									
<12	5	1.55 (1.21-1.89)	29.1	0.23	0.54	52.24 (1.44-3.04)	49.1	0.1	0.47
≥12	2	1.53 (1.21-1.86)	72.4	0.06		22.15 (-0.32-4.62)	72.8	0.06	
Geographical location									
Asia and Australia	2	1.60 (1.04-2.16)	60.7	0.08	0.86	21.52 (0.96-2.07)	21.7	0.28	<0.01
US and Europe	4	1.53 (1.02-2.05)	33.7	0.21		42.63 (1.90-3.37)	0	0.47	
Recruitment date (years)									
<1999	3	1.42 (1.07-1.77)	63.0	0.04	0.61	32.53 (1.76-3.30)	0	0.41	0.03
≥1999	3	1.77 (1.13-2.41)	0	0.53		31.75 (0.95-2.55)	45.5	0.14	
Follow-up (years)									
<6	3	1.58 (1.18-1.99)	34.1	0.22	0.46	32.09 (1.20-2.99)	61.8	0.07	0.97
≥6	3	1.56 (0.95-2.17)	50.5	0.11		32.43 (0.95-3.92)	56.1	0.08	
Cross-sectional									
Age (years)									
<2	4	1.70 (1.00-2.40)	81.0	<0.01	<0.01	42.61 (1.76-3.46)	47.0	0.13	0.12
≥12	4	2.20 (1.95-2.45)	0	0.92		44.16 (2.02-6.30)	62.6	0.05	
Geographical location									
Asia	5	1.80 (1.20-2.40)	78.3	<0.01	<0.01	52.65 (1.89-3.41)	37.3	0.17	0.17
Others	3	2.20 (1.93-2.46)	0	0.79		35.16 (1.05-9.28)	74.6	0.02	

OR, odds ratio; CI, confidence interval.

Myopia with a positive parental history is frequently assumed to have a hereditary origin, although families are known to share lifestyle behaviors as well as genes. Alternatively, there is a theory that parents with myopia, who are generally more educated, create environments that may lead to the development of myopia in their children. For instance, these parents may place higher educational demands on their children, who may therefore spent less time outdoors (14). Furthermore, parents who read extensively may also encourage their children to read more frequently (16). Since a limited number of influential factors were studied in the current analysis, further literature evidence should be quoted in order to confirm the important role of environmental factors in the development of myopia in children.

To the best of our knowledge, the current study is the first meta-analysis to estimate the association between myopia in one or two parents and a child's risk of developing the condition. A major strength of the present study is the large number of participants (n=31,677) and cases of myopia (n=8,393) from different ethnic groups that were included in the analyses, which significantly increased the statistical power of the study. Another advantage was the comprehensive and elaborate literature search that was conducted. Three comprehensive databases were searched using a wide-range of search terms.

The present meta-analysis had certain limitations. Firstly, as it is based on the results of observational studies, the possibility that other factors may explain the observed associations between parental myopia and a child's risk of developing myopia cannot be excluded. Therefore, the possibility of residual confounders remains. It is also difficult to completely rule out that either genetic factors or a shared parent-child environment was responsible for the observed associations.

Secondly, data deficits, data restriction and data of variable quality were used with varying definitions for myopia, and this may have weakened the strength of the associations observed. As myopia in parents was mainly identified using questionnaires, the possibility of recall bias and error were inevitable. The definition of childhood myopia also varied between studies and this may have resulted in an over or under estimation of the risk.

Publication bias existed in our analysis, as shown by the funnel plot and the Egger's and Begg's tests. Furthermore, the 'trim and fill' method identified possible missing studies. Nevertheless, the meta-analysis revealed that 'filled' studies did not influence the results. The OR of the pooled estimate was modified from 1.53 (95% CI, 1.21-1.85) to 1.44 (95% CI, 1.03-1.84) in cohort studies and from 1.96 (95% CI, 1.53-2.39) to 1.85 (95% CI, 1.47-2.23) in cross-sectional studies with myopia in one parent, and from 2.10 (95% CI, 1.42-2.77) to 1.79 (95% CI, 1.09-2.48) in cohort studies, and from 2.96 (95% CI, 2.21-3.71) to 2.56 (95% CI, 1.78-3.35) in cross-sectional studies with myopia in two parents.

Finally, methodological differences in the designs of the studies may have introduced heterogeneity. Following subgroup analysis, the present study revealed that geographical location and recruitment year may be possible sources of heterogeneity in the current analysis, which included cohort studies with myopia in two parents. With respect to the cross-sectional studies, age and geographical location were identified as possible sources of heterogeneity in the current analysis with myopia in one parent. Further well-designed cohort studies with adequate controls for confounding factors are required, particularly studies that allow for long-term follow-up of children as well as studies amongst populations in East Asia.

The present meta-analysis included cross-sectional and case-control studies that had small or inadequate sample sizes. This may have resulted in large effect estimates and the heterogeneous entry criteria may have limited the study results. These issues may have reduced the strength of the results obtained in the current study.

In conclusion, the present meta-analysis revealed a significant positive association between parental myopia and a child's risk of developing myopia. Furthermore, the study demonstrated that children with two myopic parents have a higher risk of developing myopia than those with one myopic parent.

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