LEADING ARTICLE

Myopia epidemiologic studies: the concept of family risk scores

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Abstract

Aim: Studies have demonstrated that there was a strong hereditary role in development of myopia. Family risk scores were developed to estimate familial risks more accurately. The reliability of the family history data was also assessed.

Materials and methods: A standardized questionnaire was developed to accurately quantify familial and other risk factors for the progression of myopia in Singapore children. 258 parents of myopic children were interviewed at a face-to-face clinic visit. Family history of myopia and severity of myopia in parents and siblings were documented. The age and sex of siblings were also noted. To assess test-retest reliability, the questionnaire was filled twice within a two week period by the parents of 30 children.

Results: The number of children with no myopic parents was 37, one myopic parent was 97, and two myopic parents was 124 . The number of children with no parents with high myopia (myopia exceeding -6.0 Diopters) was 183, one parent with high myopia was 63, and two parents with high myopia was 12 . The proportion of myopic children with more than half of the first degree relatives being myopic was 68.7%. The family risk scores were negative for 48.91%, mildly positive for 41.85%, and definitely positive for 9.24% of the children. The reliability of the questionnaire for data for family history of myopia was very good with kappa statistics ranging from 0.75 to 1.00.

Conclusion: Family risk scores that quantify proportion of family members that are myopic would be a valuable tool for evaluating familial risks for myopia. The high proportion of myopic children with positive family history scores suggests that there may be genetic attributes in the development of myopia.

Keywords: Family history, Epidemiology, Singapore, Genetics, Eye disease

Introduction

Myopia or short sightedness is one of the most common ocular disorders and its etiology has intrigued clinicians and vision scientists for centuries. The nature of environmental or genetic risk factors in man is still not known.[1-3] The strongest evidence for an environmental risk factor is for near work or any visual task performed at a close distance.[4-7] Other possible environmental risk factors include socioeconomic status as denoted by housing type, family income and occupation.[8-10] Surveys have described the prevalence of myopia in different races where Chinese and Japanese have higher rates of myopia than Caucasian and African populations.[11-14] These racial variations may be partly attributed to genetic influences or may be due to different lifestyle. Several studies have shown possible familial tendencies as quantified by parent-child correlations.[15-16] Hui *et al* investigated the role of familial risks and refraction using three indices.[16] The first index is risks and refraction using

three indices.[16] The first index is risks and refraction using three indices.[16] The first index is the Prenatal Myopic Index (PMI) which assesses parental myopia only, the second index is the Parental Refractive Index (PRI) that measures the presence of myopia and hyperopia in the child's parents, and the third index is the Familial Refractive Index that measures myopia and hyperopia in immediate relatives. Twin studies have shown a higher concordance rate of myopia in monozygotic compared to dizygotic twins.[17-19] However, it is difficult to separate the effect of genetic inheritance and the adoption of similar lifestyle within given families. Segregation analysis in Hawaii by Ashton demonstrated that myopia is inherited as a multifactorial rather than Mendelian mode of inheritance.[20] At present, no information is available from linkage analysis studies to identify the exact location of specific myopia genes.

It is important to accurately quantify familial risk factors for myopia onset and development. Most epidemiologic studies have included questions on whether the parents are myopic.[21] However, information on siblings and children of respondents is often unavailable. There are few studies that have studied all first degree relatives. Moreover, information on the age and sex of the siblings and the degree of myopia were often unavailable. The role of genetics in high myopia (myopia of > -6.0 Diopters) may be uniquely different from that of low myopia.[22] In addition, the reliability of family history data for myopia should be assessed.

Studies on other medical conditions such as rheumatoid arthritis, colorectal cancer and cardiovascular disease have developed family risk scores to assess the role of genetics for disease onset.[23-24] In a study of the familial risks for a less prevalent disease, rheumatoid arthritis, the families were classified as simplex if only the proband was affected, first degree multiplex if the proband had at least one other first degree relative that was affected, and second degree multiplex if the proband had a second degree relative that was affected.[25] For more common diseases, the proportion of relatives with the disease was noted. We have looked at several family history scores in a cohort study of the risk factors for the progression of myopia where the family history of myopia is a potential confounder as well as effect modifier. The test-retest reliability of family history data was also assessed in this study population.

Table 1. Questionnaire on family history of myopia in Singapore children aged 6 to 12 years, 1996

Please indicate whether the family member is near sighted and if present, the degree of near sightedness. Please also indicate the gender and age of each sibling.

Family member	Near-sightedness (myopia)	Degrees if short-sighted		
31 Father	yes ☐ 1 no ☐ 2 do not know ☐ 9	_ _ _ not applicable ☐ . do not know ☐ .		
32 Mother	yes ☐ 1 no ☐ 2 do not know ☐ 9	_ _ _ not applicable ☐ . do not know ☐ .		
33 Sibling 1	no sibling ☐ 0 yes ☐ 1 no ☐ 2 do not know ☐ 9	_ _ _ not applicable ☐ . do not know ☐ .	male ☐ 1 female ☐ 2	**Age** _ _
34 Sibling 2	no sibling ☐ 0 yes ☐ 1 no ☐ 2 do not know ☐ 9	_ _ _ not applicable ☐ . do not know ☐ .	male ☐ 1 female ☐ 2	_ _
35 Sibling 3	no sibling ☐ 0 yes ☐ 1 no ☐ 2 do not know ☐ 9	_ _ _ not applicable ☐ . do not know ☐ .	male ☐ 1 female ☐ 2	_ _

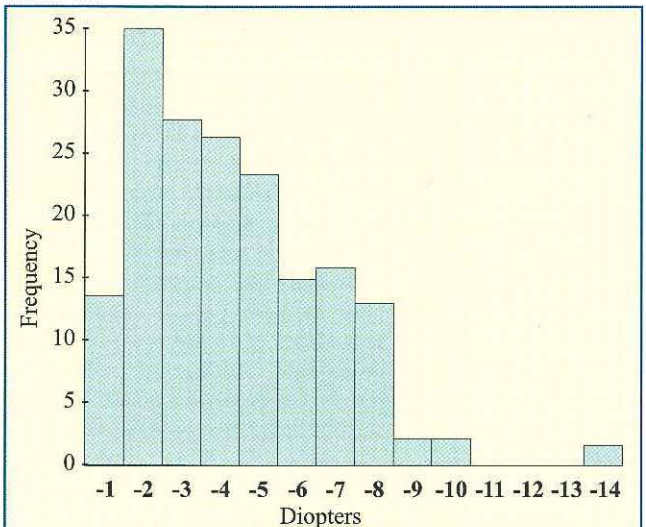

Figure 1 Refractive error of mothers with myopia of 258 myopic children in Singapore, 1996

Materials and methods

Family risk scores were developed to evaluate familial risks in a cohort study of the risk factors for the progression of myopia. Chinese children were recruited for the study from the island wide press releases. Children with chronic medical conditions and history of eye disease were excluded. 258 parents of myopic children aged 6 to 12 years in Singapore were interviewed face-to-face using a standardized pre-coded questionnaire by a single person (SSM) during their clinic visit for a screening eye examination (Table 1). The interview took approximately 15 minutes and the response rate was 100 %. This questionnaire was pilot tested in 30 students in Singapore and Baltimore and revised such that it was simple and yet maintained construct validity. The questionnaire was also filled twice by the parents of the same child within a two week period to evaluate the reliability of the data.

Information on the refractive status of all first degree relatives (parents and siblings) of the proband was obtained (Figure 1). The severity of myopia and the age as well as sex of the siblings was noted. In families where the respondents were unsure of the refractive status of family members, refractive error of the family member was assessed by noncycloplegic autorefraction with the Nidek ARK 900. The family history of myopia in the cohort was described by including the parents alone, siblings alone as well as the parents and siblings. The family history of high myopia was also contrasted with family history of low myopia. The family history scores that compared the observed number of first degree relatives with myopia with the expected number of first degree relatives with myopia was calculated. This score adjusts for family size and the age of the siblings. Thus, the prevalence rates of myopia at different ages was used to estimate the expected number of siblings with myopia for siblings of different ages.

The data was entered within one week of collection and edited manually, and information on any missing values was obtained by telephone interviews. Both descriptive and univariate analysis were conducted. The kappa statistic was used to assess the reliability of family history data. The analysis was performed using Stata version 4.0.

Results

The average age of the study population is 8.6 years (range 7 to 11 years). Figures 1 and 2 show the distribution of refractive error for father or mother who is myopic in this study population. The family history of myopia in this study population is described in several different ways. There were 37 myopic children with no myopic parents, 97 with one myopic parent and 124 with two myopic parents (Table 2). The prevalence rate of myopia for the parents is 85.7 % which is higher than the estimated 55 % in the general population.[26,27] 183 children had no parent with high myopia (myopia > -6.0 Diopters), 63 had one parent with high myopia and 12 had two parents with high myopia. Thus, 29.1 % of the parents in this study have high myopia. The distribution of family size and number of siblings in the family is described in Table 3. Figure 3 shows the distribution of family size within the study cohort. As the number of myopic first degree relatives in the family may be a biased estimate of family history if the family sizes vary and the prevalence of myopia is high in the population, we studied the proportion of family members with myopia and high myopia (Figures 4 and 5).

We also calculated family history scores comparing the observed number of first degree relatives with myopia with the expected number of first degree relatives with myopia. The family history score was negative for 48.91 %, mildly positive for 41.85 %, and definitely positive for 9.24 % of the children (Table 4). Thus, the family history of myopia for more than half of the myopic probands in this study population was higher than the general population.

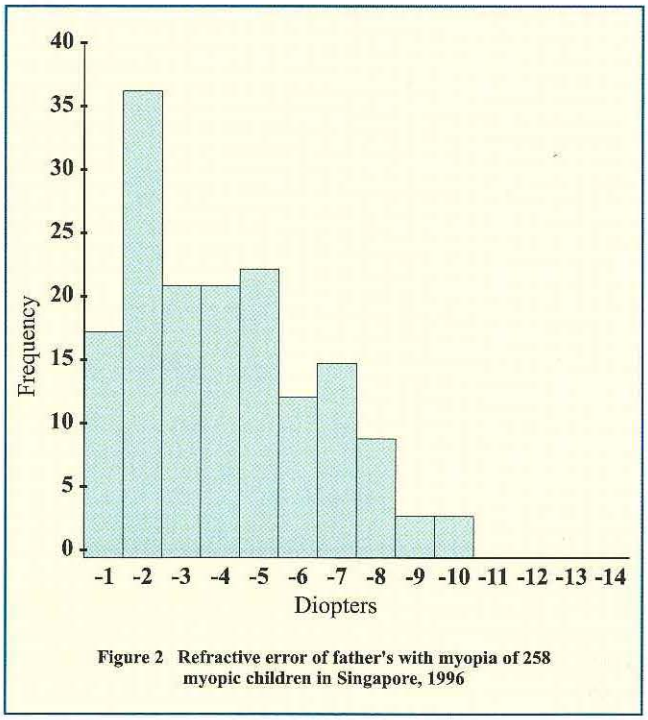

Figure 2 Refractive error of father's with myopia of 258 myopic children in Singapore, 1996

The reliability of the questionnaire data was very good and the kappa statistics ranged from 0.75 to 1.00 with a kappa of 1.00 for the myopia status in fathers (Table 5).

Discussion

Information on family history is needed to study the relationship between familial risks and progression rates for myopia. Familial risks of myopia are important confounders or effect modifiers in analytic studies of risk factors for myopia. We have developed pre-tested questionnaires to identify first degree relatives with myopia and high myopia. The reliability of this pre-tested questionnaire was very good with kappa statistics ranging from 0.75 for the size of the family to a perfect 1.00 for the myopia status in fathers. The discrepancy in family size could possibly be due to a mistaken inclusion of the proband as one of the siblings. Therefore, the family history information from the questionnaire was reproducible in the short-term and provided consistent information.

Table 2. History of myopia in parents of 258 children who are participants in a cohort study of near work and myopia progression in Singapore, 1996

Characteristics	Number	%
Number of fathers with no myopia	92	35.7
Number of fathers with myopia	166	64.3
Number of mothers with no myopia	79	30.6
Number of mothers with myopia	179	69.4
No parents with myopia	37	14.3
One parent with myopia	97	37.6
Two parents with myopia	124	48.1
No parents with high myopia	183	70.9
One parent with high myopia	63	24.4
Two parents with high myopia	12	4.7

Previous studies have quantified family history by asking for parental history of myopia. However, important information is not incorporated into the data analysis if the family history of siblings is lacking as sibling share half their genes with the proband. Both a history of myopia in parents and siblings will provide more accurate indices for family history. There have been no precise and detailed recordings of the number of myopic first degree relatives as well as the proportion of myopic individuals among first degree relatives. Family history of myopia is dependent on the family size, age of relatives and the prevalence of disease in the population. We have thus studied the proportion of myopia in first degree relatives. Furthermore, high myopia was studied separately as the genetic influences for high myopia may be higher.[22] The family size may be included as a covariate in multivariate models. The number of family members who are myopic depends on family size. Additional information on whether the siblings were full or half siblings and whether the parent's marriage was consanguineous would also be helpful.

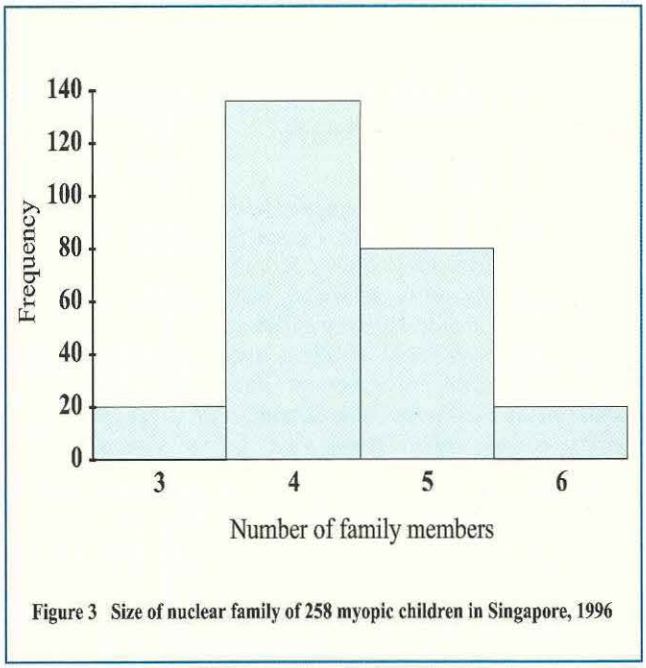

Figure 3 Size of nuclear family of 258 myopic children in Singapore, 1996

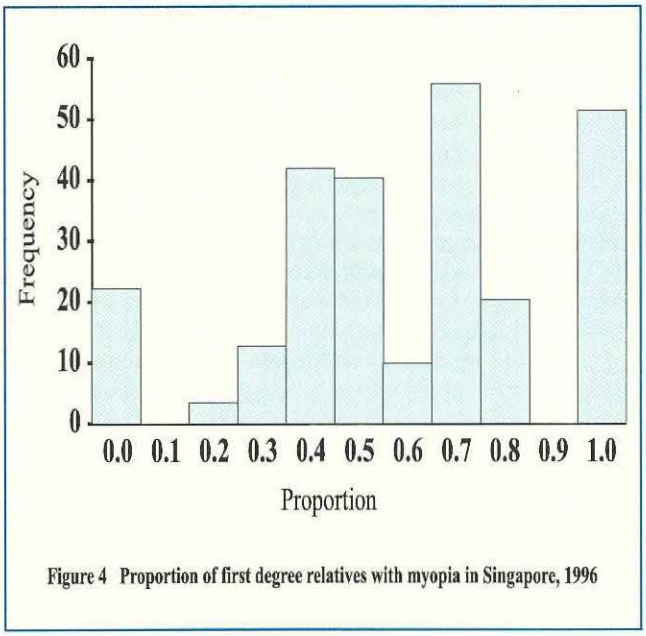

Figure 4 Proportion of first degree relatives with myopia in Singapore, 1996

Table 3. Size of family and proportion of myopic individuals in nuclear family of 258 participants of a cohort study of near work and myopia progression in Singapore, 1996

Characteristics	Number	%
No siblings with myopia	130	50.4
One sibling with myopia	111	43.0
Two siblings with myopia	13	5.0
Three siblings with myopia	4	1.6
Two first degree relatives	21	8.1
Three first degree relatives	135	52.3
Four first degree relatives	82	31.8
Five first degree relatives	20	7.8
Number with more than half of first degree relatives with myopia	177	68.7
Number with less than half of first degree relatives with myopia	81	31.3
Number with more than half of firse degree relatives with high myopia	30	11.6
Number with less than half of firse degree relatives with high myopia	228	88.4

Myopia prevalence is age dependent. A brother who is not myopic at two may have a higher contribution to familial risks compared to a brother who is not myopic but already twenty-four years of age. It is important to adjust for the age of the siblings in multivariate analyses as the contribution to familial risks are related to the age of onset of myopia in the sibling. The age of onset of myopia in each family member will also add information on the role of genetic and environment factors.

The age-dependent risk of myopia in the siblings of the proband was included in a family history score. The expected number of myopia cases for the family was obtained from an age-specific prevalence rate table and compared with the observed number of myopia cases for the family members in each family.[24] The family history score was the observed number of myopic relatives compared with the expected number of myopic relatives. In this study population where all the probands were children with myopia, the family history scores were positive for 51.1 % of the children. Thus, more than half of the study population had a family history score that was higher than that of the general population. This suggests that genetics may play a role in the development of myopia.

Table 4. Family history scores for the children in the study, Singapore, 1996

Family history score	Number	%
Negative (-1.00 to 0.5)	126	48.91
Mild positive (0.5 to 1.0)	108	41.85
Definite positive (1.0 to 2.0)	24	9.24
Very strong (2.0 to 100)	0	0

Family history score = O-E -0.5 / E where family history score is 0 if O-E $\leq$ 0.5

O = observed number of first degree relatives with myopia

E = expected number of first degree relatives with myopia calculated from prevalence rates of myopia for different ages in Singapore

Table 5. The reliability of family history data for 30 children in the study, Singapore, 1996

Variable	Kappa
Father with myopia (yes / no)	1.00
Mother with myopia (yes / no)	0.91
Number of parents with myopia	0.93
Number of family members with myopia	0.77
Family size	0.75

Pre-tested and reliable information on first degree relatives is useful in cohort, case-control or cross-sectional studies of the familial risks for myopia. Familial risks may be

quantified by evaluating the proportion of first degree relatives affected with the disease and the inclusion of the age of siblings in a multivariate model. The development of family risk scores is not only important in myopia epidemiologic research but also in analytic epidemiologic studies of other diseases that need to accurately quantify family history as a major risk factor or possible confounder. The inclusion of the family history of all first degree relatives would add valuable information to studies of the interplay between genetic and environmental causes. In addition, other methods such as segregation analysis will help to identify whether myopia is a single gene or multifactorial inheritance. Detailed molecular techniques such as linkage analysis would also further enable us to map the disease gene.

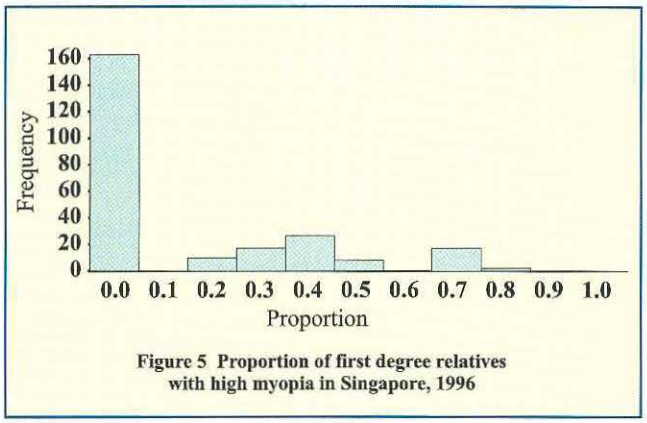

Figure 5 Proportion of first degree relatives with high myopia in Singapore, 1996

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