WORLD VIEW

Familial aggregation of myopia in the Tehran eye study: estimation of the sibling and parent–offspring recurrence risk ratios

Akbar Fotouhi, Arash Etemadi, Hassan Hashemi, Hojjat Zeraati, Joan E Bailey-Wilson, Kazem Mohammad

Br J Ophthalmol 2007;**91**:1440–1444. doi: 10.1136/bjo.2007.120162

See end of article for authors' affiliations

Correspondence to: Dr Akbar Fotouhi, Epidemiology and Biostatistics Department, School of Public Health, Tehran University of Medical Sciences, Pursina St, Keshavarz Blvd, Tehran, Iran; afotouhi@tums.ac.ir

Accepted 2 May 2007

Aim: To determine the potential influence of genetic factors on the prevalence of myopia in Tehran.
Methods: Of 6497 citizens of Tehran sampled from 160 clusters using stratified random cluster sampling, 4565 (70.3%) participated in the study and were referred to a clinic for an extensive eye examination and interview. These were from 1259 nuclear families with the average size of 3.6. Refraction data obtained from 3321 participants aged 16 years and over are presented. Three definitions of myopia, as the spherical equivalent of −0.5, −1, and −2 diopters or less, were used. Familial aggregation of myopia was evaluated with odds ratios and recurrence risk ratios (λ_R) using a multiple logistic regression with generalised estimating equations (GEE), adjusted for age, sex, height, and education.
Results: Multivariate analyses showed a strong familial aggregation of myopia among siblings (λ_R ranging from 2.09 to 3.86) and parent–offspring pairs (λ_R from 1.82 to 3.81) adjusted for age, sex, height, and education. The aggregation increased with higher myopia thresholds and with the use of cycloplegic refraction. The odds ratios for spouse pairs were not significantly different from 1.0. The association of myopia with sex, height, and education (and not age) remained significant in the final GEE2 model.
Conclusions: The findings indicate a relatively high degree of familial aggregation of myopia in the Tehran population, independent of age, sex, height, and education. This residual aggregation may be a result of heredity or of an unmeasured common environmental effect.

Several pieces of evidence have convincingly established the importance of genetic factors in the aetiology of myopia, and most studies agree that sibling correlations are stronger than those for parent–offspring comparisons.[1–4] Twin studies have shown a very high heritability for myopia,[5–7] but there is little consensus on the exact inheritance pattern.[8–15] Despite these data, environmental influences cannot be overlooked.[16–25]

While several reports, including various linkage studies, have addressed the genetics of high myopia, there is relatively little information on the role of genetics in low and moderate myopia.[26]

Recurrence risk ratios are helpful, both for determining the degree of familial aggregation of diseases and for estimating the power of genetic molecular studies,[27] provided that the potential effect of the familial aggregation of environmental risk factors is taken into account and ascertainment bias and overreporting are avoided.[28] Most studies have focused on the sibling recurrence risk ratio (λ_s).[29] However, measuring familial aggregation among other family members can be helpful in determining possible mechanisms of familial disease patterns.[30]

In Iran, the prevalence of myopia is about 22% in the general population.[31] Little is known about the familial aggregation of myopia in the Iranian population. Our aim in this study was to determine the potential influence of genetic and environmental factors on the prevalence of myopia among the Tehran eye study population above the age of 15, using different thresholds for defining myopia. This age group was selected because it would yield a relatively homogeneous sample with stable refraction. Logistic regression models, using generalised estimating equations (GEE), were used to allow for familial correlation of myopia and its risk factors in calculating the recurrence risks.

METHODS

The Tehran eye study is a population based cross sectional study. Detailed descriptions of the methodology have already been published[32 33] and are summarised here. The sampling strategy followed a stratified cluster sampling procedure with proportional allocation within strata. The survey target population comprised non-institutionalised urban citizens of all ages residing in Tehran city in 2002 (only those above 15 were used for analysis in this report). The sample stratification was done according to the 22 municipal districts of Tehran city, proportional to the number of households. In all, 160 clusters were randomly selected, based on block enumeration of the national census of 1996 by the Statistical Centre of Iran. A team consisting of two interviewers described the project to each household, and invited all household members for a complete eye examination at Noor Vision Correction Centre.

Refraction was measured for all participants using a Topcon automated refractometer (Topcon KR 8000, Topcon Corporation, Tokyo, Japan). Results from autorefraction were used as a starting point for full subjective and manifest refraction. When autorefraction was not possible (especially if there was media opacity), manual manifest and subjective refraction was attempted. If the ophthalmologist found no contraindication, cycloplegic refraction was done. In this case, one drop of cyclopentolate (1%) was instilled 30 and 25 minutes before refraction. The participants were informed about the symptoms resulting from cyclopentolate use.

All observers received regular quality control visits from the project manager. In addition, interobserver comparison of refraction measurements in 538 eyes during the study showed

Abbreviations: GEE, generalised estimating equations; GEE2, second order generalised estimating equations

that the intraclass correlation coefficient of reliability was 0.98 (95% confidence interval (CI), 0.97 to 0.99) for manifest spherical equivalent refraction.

The study followed the tenets of the declaration of Helsinki. The research and ethics committee of the Noor Vision Correction Centre and the ethics committee of the National Research Centre for Medical Sciences approved the study. All participants were informed about the project and the procedures in their native language before being enrolled. The participant's agreement for examination was obtained verbally.

Statistical methods

Myopia was defined as the spherical equivalent of −0.5 diopters (D) or less. We further used two other myopia thresholds (−1 D and −2 D) to investigate the familial aggregation in higher levels of myopia. As the spherical equivalents in the right and left eyes were highly correlated (Pearson's correlation, $r = 0.84$, $p<0.001$) we present the data for right eyes only.

In calculating standard errors and 95% confidence intervals, the cluster sampling design was taken into account.[34] The age and sex distributions of participants were different from the city's general population in that people over 40 years of age and women were overrepresented. For this reason, rates were directly age and sex standardised to the 1996 Tehran population using data from the Iranian Statistics Centre.[35]

For analysis of familial aggregation, the method described by Liang and Beaty[36] was used. In this method, the odds ratios estimated between family members are independent of family size. The following notation applies:

Let J be the number of families included in the analysis. For a single family of size n_j ($j = 1, \ldots, J$) we denote with y_{ij} the binary outcome (0–1) of the ith individual in family j. The odds ratio between the ith and the kth family member in the jth family is:

$$OR_{ikj} = \frac{Pr\,(Y_j=1, Y_k=1)/Pr\,(Y_j=0, Y_k=1)}{Pr\,(Y_j=1, Y_k=0)/Pr\,(Y_j=0, Y_k=0)}$$

For statistical modelling we estimated the log odds ratio within an appropriate regression model. Three different myopia thresholds (−0.5, −1.0, and −2.0 D) were used in the model. A second order generalised estimating equation (GEE2) was used for adjustments to odds ratios for environmental risk factors, which simultaneously models the risk of a person having myopia and the familial associations. The estimation of the parameters has been discussed in detail by Liang and Zeger,[37] and Liang *et al*.[38] Only full siblings and their parents were included in the analysis. The risk factors used in the models were age, sex, height, and education.

Recurrence risk ratios, defined as the risk of being affected given an affected family member relative to the risk in the population, were calculated using odds ratios from the GEE2 model,[26] as follows:

$$\lambda_R = \frac{1}{p}\,\frac{OR\,(p/1-p)}{p[1+OR(p/(1-p))]}$$

where p is the estimated population prevalence of myopia. For each threshold used in the GEE2 model, the corresponding prevalence in our data was used for estimation of λ_R.

RESULTS

Between August and December 2002, 4565 of the 6497 eligible individuals in the sample completed the interview and the ophthalmic examination (a participation rate of 70.3%). These were from 1259 nuclear families with an average size of 3.6 individuals. Of the 4565 participants, 3321 were above 15 years of age. Data are presented only for these. The study sample consisted of 1298 men (39.1%) and 2023 women (60.9%) between 16 and 96 years of age, with a mean (SD) age of 37.8 (16.2) years.

Manifest refraction data were not obtained for 81, leaving 3240 right eyes available for analysis. Of the 81 people excluded, 44 (54.3%) had a previous history of cataract, refractive surgery, and media opacities in their right eyes. Refraction was not carried out in the others (37; 45.7%) because of poor cooperation or refusal. Forty six participants had contraindications to cycloplegic refraction and 540 others refused to have it. Cycloplegic refraction was done in the remaining 2735 participants.

Table 1 presents the age and sex specific prevalence of myopia, using the −0.5 cut off. Overall, the prevalence of myopia was 26.2% based on manifest refraction and 20.5% based on cycloplegic refraction. Myopia was significantly related to age ($p<0.001$): its prevalence decreased significantly with increasing age (both sexes combined) from the 16–25 to the 36–45 year age groups, and then remained almost steady.

A significant association between myopia and educational level was found (table 2): myopia was found to be more prevalent among individuals with higher educational levels. Comparing the different ethnic groups in this study, we found that the prevalence of myopia was not significantly affected by ethnicity (data not shown).

The associations of myopia between family members using GEE2 and adjusted for age, sex, education, and height are presented in table 3. The details of these associations are presented by odds ratios and recurrence risk ratios (λ_R) among different family pairs. The analyses yielded odds ratios of 3.42 (manifest) and 4.35 (cycloplegic) for the association of myopia (defined as −0.5 D or less) among siblings, which correspond to recurrence risk ratios of 2.09 and 2.58, respectively. Among parent–offspring pairs, using the same definition of myopia, odds ratios of 2.56 ($\lambda_R = 1.82$) for manifest myopia and 2.80 ($\lambda_R = 2.05$) for cycloplegic myopia were observed. The odds ratios and recurrence risk ratios increased with higher myopia thresholds in both family relation types. Cycloplegic myopia also showed a higher degree of familial aggregation; thus the highest odds ratios were seen for myopia defined as cycloplegic refraction below −2 D (5.31 for sibling–sibling pairs, and 5.21 for parent–offspring pairs ($\lambda_R = 3.86$ and 3.81, respectively)). The sibling–sibling odds ratios were higher than the parent–offspring odds ratios in all models, but the differences were less pronounced for cycloplegic refraction. The odds ratios for spouse pairs were not significantly different from 1.0.

In the multivariable analyses, the association of myopia with sex, height, and education (and not age) remained significant in the final GEE2 model (data not shown).

DISCUSSION

In this study, siblings and offspring of a myopic person had, on average, a three to five times greater chance of being myopic than people without such a myopic relative. However, spouses of a myopic individual were not at significantly increased risk.

In a reanalysis of available data from Danish and American studies, Guggenheim and colleagues[29] estimated the sibling recurrence risk ratio (λ_s) to be 20 for high myopia and 1.5 for low myopia. These two figures came from two different populations and were generated using backward analysis of published reports. In another study, Farbrother *et al*[27] showed a λ_s of 4.5 for high myopia in a sample of English families. In that study, refractive errors were not measured directly and instead, age at onset of myopia was used as an estimator. The above studies were dependent on probands for sampling families, leading to an overestimation of familial aggregation from ascertainment bias.[39] Lack of adjustment for other myopia risk factors may also have given rise to high estimates of familial

Table 1 Prevalence of myopia defined as −0.5 D or less, by sex and age, based on manifest and cycloplegic refraction*

Subjects and age groups (years)	Manifest refraction		Cycloplegic refraction	
	No	Per cent (95% CI)	No	Per cent (95% CI)
Men				
16–25	354	28.2 (23.1 to 33.3)	284	21.6 (16.8 to 26.5)
26–35	236	29.7 (22.7 to 36.8)	184	19.0 (12.3 to 25.6)
36–45	237	21.5 (16.5 to 26.6)	172	18.0 (12.5 to 23.5)
46–55	190	19.1 (13.6 to 24.6)	166	15.5 (10.2 to 20.8)
56+	242	20.7 (15.8 to 25.6)	215	20.2 (15.1 to 25.2)
Women				
16–25	620	30.4 (26.5 to 34.3)	536	23.3 (19.7 to 27.1)
26–35	402	27.5 (23.2 to 32.0)	333	19.5 (14.9 to 24.1)
36–45	406	24.0 (19.6 to 28.4)	354	20.0 (15.5 to 24.5)
46–55	336	27.1 (22.8 to 31.3)	298	24.5 (20.0 to 28.9)
56+	216	25.7 (19.8 to 31.7)	193	23.2 (16.7 to 29.6)
Men and women				
16–25	974	29.3 (26.0 to 32.7)	820	22.5 (19.2 to 25.9)
26–35	639	28.7 (24.4 to 33.1)	517	19.2 (14.9 to 23.5)
36–45	643	22.7 (19.5 to 26.0)	526	19.1 (15.7 to 22.4)
46–55	526	23.2 (19.7 to 26.6)	464	20.1 (16.8 to 23.5)
56+	458	23.0 (19.3 to 26.7)	408	22.5 (17.6 to 25.5)
All ages				
Men	1260	25.1 (22.2 to 28.0)	1021	19.3 (16.5 to 22.1)
Women	1980	27.4 (25.2 to 29.6)	1714	21.8 (19.4 to 24.2)
All	3240	26.2 (24.4 to 28.0)	2735	20.5 (18.6 to 22.4)

*Age and sex standardised to the 1996 Tehran population.
CI, confidence interval.

aggregation because of a shared environment. Lee *et al*[3] found odds ratios of 2.82 to 4.25 for myopia less than −0.5 D among sibling pairs from the Beaver Dam population (mean age 61.5 years). Wojciechowski and colleagues,[26] as part of a population based study, reported λ_s for different thresholds of low to moderate myopia in an elderly population (mean age 73.4 years) using a GEE2 model. The recurrence risk ratios in this study ranged between 1.90 and 2.52 depending on the definition used for myopia. The studies in elderly populations might underestimate the effect of heredity in favour of stronger environmental influence associated with aging.[26] We showed higher estimates of recurrence risk and odds ratios in the present study, and a more marked increase in higher cut off points for myopia. While the genetic mechanisms of high myopia are now better understood, our results add to the evidence that both low to moderate and high myopia are part of a spectrum that is at least partly determined by complex genetic influences.[3 6 26 40]

Most previous studies have only reported the recurrence risk of myopia among siblings. The familial aggregation found in this study was greater among siblings than between parents and offspring. Similarly, the familial occurrence of myopia has been noted by several investigators to be greatest between siblings and less between parents and offspring.[2–4] This suggests that shared environmental factors could be important in the aggregation of myopia.[29] There may also be a cohort effect, caused by an increased amount of close up work activity in younger generations.[9] This is supported by the observation of increased myopia prevalence in the younger age groups.[41] Findings from the Framingham Offspring Eye Study Group also showed that myopia was less aggregated in siblings with a larger age difference.[42] Like many others, we showed a strong association between education and the prevalence of myopia.[4 19–20] However, it remains unclear whether educational level is an independent risk factor or a surrogate for close up work or some other socioeconomic characteristic.[20–21] The amount of near work seems to have increased in recent years, even at the same educational level.[9]

Table 2 Prevalence of myopia defined as −0.5 D or less based on manifest refraction, by education level*

	No	Per cent (95% CI)
Illiterate	264	18.5 (15.0 to 22.0)
Primary school	345	20.1 (14.8 to 25.4)
High school not completed	846	21.3 (18.7 to 23.9)
High school diploma	1078	23.5 (20.7 to 26.3)
College or graduate school	685	34.0 (29.5 to 38.5)

*Age and sex standardised to the 1996 Tehran population.
CI, confidence interval.

Although the results of cycloplegic refraction were consistent with those of manifest refraction, the degree of the observed aggregation was higher with cycloplegic refraction. This was not due to decreased prevalence, as such a decrease can only influence recurrence risk ratios and not odds ratios. It has been shown that manifest and subjective refraction tend to show more negative results than cycloplegic refraction,[43 44] which is supported by the lower prevalence of cycloplegic versus manifest myopia in our study. Thus, by reducing the number of false positive results and the resultant non-differential misclassification, cycloplegic refraction can lead to less biased odds ratio estimates which are further from the null.[45]

The relations between refractive error and height or weight are unconvincing, although eye size may be linked to body stature.[25] In our data, height had a significant effect in the model, but it did not affect the odds ratios from familial aggregation. No association was found between myopia and ethnicity in these data, which might reflect the lack of sufficient ethnic heterogeneity in our population.

GEE models are used increasingly to analyse correlated data (such as family studies), especially when they are binary or in the form of counts.[46] The use of the extended form of this method (GEE2) made it possible to account for multiple within-family associations and various family sizes while adjusting for environmental determinants of myopia.[36] On the other hand, some other risk factors for myopia—such as near work, night lighting, intelligence, socioeconomic status, and nutrition—were not studied in this population.[23]

Table 3 Familial relations of myopia in multivariable regression using GEE2 method for different definitions of myopia

	Manifest refraction		Cycloplegic refraction	
	Adjusted OR* (CI 95%)	λ_R	Adjusted OR (CI 95%)	λ_R
Myopia $\leqslant -0.5$ D				
Sibling–sibling	3.42 (1.99 to 5.81)	2.09	4.35 (1.97 to 9.58)	2.58
Parent–offspring	2.56 (1.88 to 3.49)	1.82	2.80 (1.88 to 4.22)	2.05
Spouse	0.79 (0.51 to 1.22)	0.84	0.68 (0.38 to 1.23)	0.73
Myopia $\leqslant -1$ D				
Sibling–sibling	3.93 (2.16 to 7.10)	2.67	3.25 (1.75 to 5.99)	2.46
Parent–offspring	3.03 (2.09 to 4.35)	2.26	3.22 (2.09 to 4.95)	2.45
Spouse	0.99 (0.57 to 1.75)	0.99	1.19 (0.59 to 2.34)	1.15
Myopia $\leqslant -2$ D				
Sibling–sibling	4.39 (2.20 to 8.76)	3.32	5.31 (2.43 to 11.59)	3.86
Parent–offspring	3.53 (2.18 to 5.75)	2.84	5.21 (3.03 to 9.03)	3.81
Spouse	0.87 (0.35 to 2.18)	0.88	1.02 (0.35 to 3.03)	1.02

*All models were adjusted for age, sex, years of education, and height as possible confounding variables (data not shown).
CI, confidence interval; GEE2, second order generalised estimating equations; OR, odds ratio.

The genetics of myopia are complex and it is rarely possible to find families showing a clear cut monofactorial (Mendelian) inheritance pattern. While extremes of refractive error, such as high myopia, are more likely to have a simple mode of inheritance, refractive error occurs as a continuum across the population and seems likely to be multifactorial in origin, with a complex mode of inheritance. Segregation analysis studies by Klein *et al*[9] and Ashton[47] suggest that the trait may be multifactorial, and analyses in our population could help to clarify the mode of inheritance in this population.

Our findings indicate a relatively high degree of familial aggregation, independent of age, sex, height, and education, in the Tehran population. This residual aggregation may be the result of heredity or the effect of undetermined common environmental factors.

ACKNOWLEDGEMENTS

This project was funded in part by the Noor Vision Correction Centre and a grant from the Iranian National Research Centre for Medical Sciences, and in part by the intramural programme of the National Human Genome Research Institute, National Institutes of Health, USA.

Authors' affiliations

Akbar Fotouhi, Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
Arash Etemadi, Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences
Hassan Hashemi, Farabi Eye Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, and Noor Vision Correction Centre, Tehran
Hojjat Zeraati, Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences
Joan E Bailey-Wilson, Inherited Disease Research Branch, National Human Genome Research Institute, Baltimore, Maryland, USA
Kazem Mohammad, Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences

Competing interests: None declared.

REFERENCES

1 **Goldschmidt E**. The mystery of myopia. *Acta Ophthalmol Scand* 2003;**81**:431–6.
2 **Saw SM**, Katz J, Schein OD, *et al.* Epidemiology of myopia. *Epidemiol Rev* 1996;**18**:175–87.
3 **Lee KE**, Klein BE, Klein R, *et al.* Aggregation of refractive error and 5-year changes in refractive error among families in the Beaver Dam Eye Study. *Arch Ophthalmol* 2001;**119**:1679–85.
4 **Rose KA**, Morgan IG, Smith W, *et al.* High heritability of myopia does not preclude rapid changes in prevalence. *Clin Exp Ophthalmol* 2002;**30**:168–72.
5 **Hammond CJ**, Andrew T, Mak YT, *et al.* A susceptibility locus for myopia in the normal population is linked to the PAX6 gene region on chromosome 11: a genomewide scan of dizygotic twins. *Am J Hum Genet* 2004;**75**:294–304.
6 **Hammond CJ**, Snieder H, Gilbert CE, *et al.* Genes and environment in refractive error: the twin eye study. *Invest Ophthalmol Vis Sci* 2001;**42**:1232–6.
7 **Lyhne N**, Sjolie AK, Kyvik KO, *et al.* The importance of genes and environment for ocular refraction and its determiners: a population based study among 20–45 year old twins. *Br J Ophthalmol* 2001;**85**:1470–6.
8 **Wissinger B**, Kohl S, Langenbeck U. Genetics in ophthalmology. *Dev Ophthalmol* 2003;**37**:34–49.
9 **Klein AP**, Duggal P, Lee KE, *et al.* Support for polygenic influences on ocular refractive error. *Invest Ophthalmol Vis Sci* 2005;**46**:442–6.
10 **Young TL**, Ronan SM, Drahozal LA, *et al.* Evidence that a locus for familial high myopia maps to chromosome 18p. *Am J Hum Genet* 1998;**63**:109–19.
11 **Young TL**, Ronan SM, Alvear AB, *et al.* A second locus for familial high myopia maps to chromosome 12q. *Am J Hum Genet* 1998;**63**:1419–24.
12 **Naiglin L**, Gazagne C, Dallongeville F, *et al.* A genome wide scan for familial high myopia suggests a novel locus on chromosome 7q36. *J Med Genet* 2002;**39**:118–24.
13 **Paluru P**, Ronan SM, Heon E, *et al.* New locus for autosomal dominant high myopia maps to the long arm of chromosome 17. *Invest Ophthalmol Vis Sci* 2003;**44**:1830–6.
14 **Edwards M**, Lewis WH. Autosomal recessive inheritance of myopia in Hong Kong Chinese infants. *Ophthalmic Physiol Opt* 1991;**11**:227–31.
15 **Schwartz M**, Haim M, Skarsholm D. X-linked myopia: Bornholm eye disease: linkage to DNA markers on the distal part of Xq. *Clin Genet* 1990;**38**:281–6.
16 **Saw SM**. A synopsis of the prevalence rates and environmental risk factors for myopia. *Clin Exp Optom* 2003;**86**:289–94.
17 **Wu HM**, Seet B, Yap EP, *et al.* Does education explain ethnic differences in myopia prevalence? A population-based study of young adult males in Singapore. *Optom Vis Sci* 2001;**78**:234–9.
18 **Rosner M**, Belkin M. Intelligence, education, and myopia in males. *Arch Ophthalmol* 1987;**105**:1508–11.
19 **Saw SM**, Wu HM, Seet B, *et al.* Academic achievement, close up work parameters, and myopia in Singapore military conscripts. *Br J Ophthalmol* 2001;**85**:855–60.
20 **Teikari JM**. Myopia and stature. *Acta Ophthalmol (Copenh)* 1987;**65**:673–6.
21 **Shimizu N**, Nomura H, Ando F, *et al.* Refractive errors and factors associated with myopia in an adult Japanese population. *Jpn J Ophthalmol* 2003;**47**:6–12.
22 **Attebo K**, Ivers RQ, Mitchell P. Refractive errors in an older population: the Blue Mountains Eye Study. *Ophthalmology* 1999;**106**:1066–72.
23 **Wong TY**, Foster PJ, Johnson GJ, *et al.* The relationship between ocular dimensions and refraction with adult stature: the Tanjong Pagar Survey. *Invest Ophthalmol Vis Sci* 2001;**42**:1237–42.
24 **McBrien NA**, Adams DW. A longitudinal investigation of adult-onset and adult progression of myopia in an occupational group. *Invest Ophthalmol Vis Sci* 1997;**38**:321–33.
25 **Simensen B**, Thorud LO. Adult-onset myopia and occupation. *Acta Ophthalmol (Copenh)* 1994;**72**:469–71.
26 **Wojciechowski R**, Congdon N, Bowie H, *et al.* Heritability of refractive error and familial aggregation of myopia in an elderly American population. *Invest Ophthalmol Vis Sci* 2005;**46**:1588–92.
27 **Farbrother JE**, Kirov G, Owen MJ, *et al.* Family aggregation of high myopia: estimation of the sibling recurrence risk ratio. *Invest Ophthalmol Vis Sci* 2004;**45**:2873–8.
28 **Guo SW**. Familial aggregation of environmental risk factors and familial aggregation of disease. *Am J Epidemiol* 2000;**151**:1121–31.
29 **Guggenheim JA**, Kirov G, Hodson SA. The heritability of high myopia: a reanalysis of Goldschmidt's data. *J Med Genet* 2000;**37**:227–31.
30 **Liang KY**, Beaty TH. Statistical designs for familial aggregation. *Stat Methods Med Res* 2000;**9**:543–62.

31 **Hashemi H**, Fotouhi A, Mohammad K. The age- and gender-specific prevalences of refractive errors in Tehran: the Tehran Eye Study. *Ophthalmic Epidemiol* 2004;**11**:213–25.
32 **Hashemi H**, Fotouhi A, Mohammad K. Tehran Eye Study: research design and eye examination protocol. *BMC Ophthalmology* 2003;**3**:8.
33 **Fotouhi A**, Hashemi H, Mohammad K. The prevalence and causes of visual impairment in Tehran: the Tehran Eye Study. *Br J Ophthalmol* 2004;**88**:740–5.
34 **Bennett S**, Woods T, Liyanage WM, *et al*. A simplified method for cluster sample surveys of health in developing countries. *World Health Stat Q* 1991;**44**:98–106.
35 **Iranian Statistics Centre**. The report of the 1996 population census. http://amar.sci.or.ir (10 March 2003).
36 **Liang KY**, Beaty TH. Measuring familial aggregation by using odds-ratio regression models. *Genet Epidemiol* 1991;**8**:361–70.
37 **Liang KY**, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986;**73**:13–22.
38 **Liang KY**, Zeger SL, Qaqish BF. Multivariate regression analyses for categorical data. *J R Stat Soc* 1992;**54**:3–40.
39 **Khoury MJ**, Beaty TH, Cohen BH. *Fundamentals of genetic epidemiology*. New York: Oxford University Press, 1993:238–42.
40 **Alsbirk PH**. Refraction in adult West Greenland Eskimos: a population study of spherical refractive errors, including oculometric and familial correlations. *Acta Ophthalmol (Copenh)* 1979;**57**:84–95.
41 **Rose K**, Smith W, Morgan I, *et al*. The increasing prevalence of myopia: implications for Australia. *Clin Experiment Ophthalmol* 2001;**29**:116–20.
42 **The Framingham Offspring Eye Study Group**. Familial aggregation and prevalence of myopia in the Framingham Offspring Eye Study. *Arch Ophthalmol* 1996;**114**:326–32.
43 **Choong YF**, Chen AH, Goh PP. A comparison of autorefraction and subjective refraction with and without cycloplegia in primary school children. *Am J Ophthalmol* 2006;**142**:68–74.
44 **Zhao J**, Mao J, Luo R, *et al*. Accuracy of noncycloplegic autorefraction in school-age children in China. *Optom Vis Sci* 2004;**81**:49–55.
45 **Szklo M**, Nieto FJ. *Epidemiology: beyond the basics*, 2nd edition. Sudbury, MA: Jones and Bartlett, 2007:121–33.
46 **Hanley JA**, Negassa A, Edwardes MD, *et al*. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol* 2003;**157**:364–75.
47 **Ashton G**. Segregation analysis of ocular refraction and myopia. *Hum Hered* 1985;**35**:232–9.