Title: **Risk factors for childhood myopia: findings from the NICER study**

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Grant Information:

College of Optometrists, London. The sponsor or funding organization had no role in the design or conduct of this research.

Word Count:2836

Abstract

Purpose:

To explore risk factors for myopia in 12-13-year-old children in Northern Ireland (NI).

Methods:

Stratified random sampling was performed to obtain representation of schools and children.

Cycloplegia was achieved using cyclopentolate hydrochloride 1%. Distance autorefraction was measured using the Shin-Nippon SRW-5000. Height and weight were measured. Parents and children completed a questionnaire including questions on parental history of myopia, sociodemographic factors, childhood levels of near vision and physical activity to identify potential risk factors for myopia. Myopia was defined as spherical equivalent ≤-0.50D in either eye.

Results:

Data from 661 white children aged 12-13-years showed that regular physical activity was associated with a lower estimated prevalence of myopia as compared with sedentary lifestyles (odds ratio (OR) =0.46 adjusted for age, sex, deprivation score, family size, school type, urbanicity, 95%CI 0.23 to 0.90, p for trend = 0.027). The odds of myopia were more than 2.5 times higher amongst children attending academically-selective-schools (adjusted OR=2.66, 95%CI 1.48 to 4.78) compared to non- academically-selective-schools. There was no evidence of an effect of urban versus non-urban environment on the odds of myopia. Compared to children with no myopic parents, children with one or both parents being myopic were 2.91 times (95%CI 1.54 to 5.52) and 7.79 times (95%CI 2.93 to 20.67) more likely to have myopia, respectively.

Conclusions:

In NI children parental history of myopia and type of schooling, are important determinants of myopia. The association between myopia and an environmental factor such as physical activity levels may provide insight into preventive strategies.

Risk factors for childhood myopia: findings from the NICER study

Introduction

Although myopia can be corrected with spectacles, contact lenses or refractive surgery the costs of treating myopia and its associated co-morbidities including glaucoma, rhegmatogenous retinal detachment and chorio-retinal atrophy can be considerable and is conservatively estimated to be in excess of $4.6 billion dollars in the United States.[1, 2] In the UK alone there are approximately 200,000 people with pathological myopia. [National Institute for Health and Care Excellence http://www.nice.org.uk/guidance/ta298/resources/choroidal-neovascularisation-pathological-myopia-ranibizumab-draft-scope-pre-referral2, date accessed 9th July 2014] There is therefore considerable interest in the identification of risk factors for myopia[3] as modifying these risk factors may lessen the prevalence and impact of myopia. Many genetic and environmental factors have been shown to be associated with the prevalence of myopia including higher educational attainment,[4] greater amounts of near work,[4, 5] socio-economic status,[6, 7] body stature,[8] degree of urbanisation,[9] level of physical activity,[10] level of outdoor activity,[3] low birth weight,[11] parental smoking status,[12] parental education and birth order[13] and lack of breastfeeding.[14] Family history of myopia[15-18] and ethnicity[15, 16, 19, 20] are also recognized risk factors for myopia and associations with age and gender have also been described.[21] Numerous narrative reviews describe these risk factors in some detail.[22-25]

Despite the extensive list of environmental factors that may influence the development of myopia they can only explain a small proportion of the variability found in myopia prevalence and conflicting evidence exists for the association of many of the risk factors including increased near work[15] and breast-feeding.[13] Some individuals may also have a genetic predisposition resulting in greater susceptibility to the environmental influences associated with myopia,[26] which may partly explain worldwide variation in myopia prevalence.[23]

The Northern Ireland Childhood Errors of Refraction (NICER) study, an epidemiological survey of childhood refractive status has shown that there is a high prevalence of myopia in white children in Northern Ireland (NI) compared with similarly aged white children in Australia.[27] Reasons for this difference are unclear. This paper explores the NICER study data and aims to describe the association between some of the putative risk factors, including family history and environmental factors, and myopia in 12-13-year-old children in Northern Ireland.

Methods

Approval for the study was obtained from the University of Ulster's Research Ethics Committee. The research adhered to the principles of the Declaration of Helsinki.

The methodology of the NICER study has previously been described in detail.[28] In summary, data on population density and economic deprivation (Multiple Deprivation Measure) (http://www.nisra.gov.uk/) were used to broadly classify schools into four strata of urban/rural and deprived/not deprived. Stratified random sampling of schools was performed to obtain representation of schools and children across these four strata from four local government districts in the North and West of Northern Ireland. Informed consent was obtained from a parent or other responsible adult and the child themselves before the child's participation in the study.

Two or more classes of 12-13-year old children from fifteen schools were invited to participate in the study. The children were tested within school premises during the school day. Children completed a questionnaire designed to identify risk factors for myopia, including amount of time spent on near work and level of physical activity. The protocol for data collection included cycloplegia of both eyes using one drop of cyclopentolate hydrochloride 1% (Minims single dose, Chauvin Pharmaceuticals, Romford, UK) after instillation of one drop of proxymetacaine hydrochloride 0.5% (Minims single dose, Chauvin Pharmaceuticals). Distance autorefraction was measured using the binocular openfield autorefractor, the Shin-Nippon SRW-5000 (Shin-Nippon, Tokyo, Japan), at least 20 minutes after the instillation of the eye drops. The representative value as determined by the instrument was used in subsequent analyses. Height (in centimetres) was measured using the Leicester Height Measure (SECA, Hamburg, Germany) and weight (in kilograms) was assessed using Tanita digital scales, model HD-327 (Tanita, Middlesex, UK). After the examination the child's parents/guardians were asked to complete a detailed questionnaire, including sociodemographic characteristics, parental factors and birth history.

Definitions

All children with spherical equivalent of less or equal to -0.50D in either eye were classified as myopic.

Childhood risk factors

Age (in months), sex and body size were recorded. Children were categorised as *normal weight*, *overweight* or *obese* by applying the body mass index (BMI) cut-offs at half yearly intervals for boys and girls as recommended by the Childhood Obesity Working Group of the International Obesity Taskforce (Table 4 as published by Cole et al in 2000).[29] Self reported levels of physical activity, time spent doing near visual tasks (including homework, screen-time), number of child siblings and older siblings (and hence younger siblings) were obtained from child and parental questionnaires. Data from child questionnaires were used in preference. Attendance at a grammar or other school was also noted; in NI entrance to grammar school is at age 11 years and is determined by performance in an academic examination. This is a competitive academic process and proximity to the school is not used as a criterion for entrance. Approximately 42% of children attend a grammar school (http://www.deni.gov.uk/). Non-grammar schools do not use academic criteria for entrance.

Parental risk factors

Parental education was classified as *low* (no post-secondary education, Ordinary levels (General Certificate of Secondary Education)/Business and Technology Education Council, BTec), *medium* (General Certificate of Education Advanced Levels/Higher National Certificate (HNC), National Vocational Qualifications (NVQ), City and Guilds, Diploma/Higher National Diploma (HND), Ordinary National Diploma (OND), Royal Society of the Arts (RSA), Ordinary National Certificate (ONC) or *high* (Degree/Post Graduate Certificate in Education (PGCE), higher degree). The highest maternal or paternal education (low, medium, high) reported in the household was used.

Parental myopia was classified depending on the number of parents who self-reported being myopic as (i) none, (ii) one parent myopic and (iii) both parents myopic

Sociodemographic characteristics

Assessment of socio-economic status was made using the deprivation rank of the child's place of residence. Each child's home address postcode was used to place the child's home into a small scale census Output Area, allowing a Northern Ireland multiple deprivation measure (NIMDM) to be applied to each child. The Output Area Level is based on three weighted domains of deprivation: income (47%), employment (41.7%) and proximity to services (16.6%). This continuous variable for socio-economic status (SES) was converted into a categorical variable with five categories using quintiles of SES.

Children were classified as living in urban or rural areas depending on the population density of the area in which they resided. Wards with a population density of less than 10 persons per hectare (equivalent to 1000 persons per km^2) were classified as rural and those with a population density of at least 10 persons or more per hectare were classified as urban. This cut was used to ensure that we sampled children living in rural (on average 1 person per hectare) as well as urban areas (on average 23 persons per hectare).

Statistical methods

All statistical analyses were performed using Stata (StataCorp, Texas, USA). Continuous variables were summarised by means and standard deviations, whilst categorical variables were summarized by frequencies along with the percentage of myopes in each group. All statistical tests were performed using 5% as the level of statistical significance.

Multilevel mixed-effects logistic regression was used to investigate associations between the odds of myopia in either eye and potential risk factors, including age (per year increase in age), gender, birth weight (per Kg increase in birth weight), current obesity level (measured by BMI or BMI group according to the IOTF classification in children), economic deprivation score (in quintiles; 1: most deprived, 5: least deprived), self-reported physical activity levels, self-reported levels of carrying out near visual tasks (including screen-time and time spent on homework), family size of the child (by including the number of younger and number of older siblings in the same model captures the combined effects family size (number of younger siblings + number of older siblings) and birth order (number of older siblings) using two variables that are independent of each other), parental reported myopia and education, child's place of birth (NI or elsewhere), whether the child lived in an urban or rural environment, and type of school attended (grammar, non-grammar). All analyses included school as a random effect to take account of clustering of children within schools.

All risk factors associated with myopia in univariate analyses were included in the final model, along with established risk factors for myopia (age, gender, urban/rural living environment). An exception was made for variables with a considerable amount of missing values (i .e. more than 30% missing). Missing values occurred due to non-completion of the questionnaire or missing information on place of residence of the child.

Results

Of the children invited to participate in the study, parental consent was obtained from 65%. Indicative of the Northern Irish population, 98.7% were white and this report presents data from 661 white children aged 12-13-years, 117 (17.7%) of whom were myopic.

Table 1 provides a summary of the available data along with the odds ratios associated with each risk factor of myopia obtained by analysing each factor separately. Birth weight, place of birth, parental myopia and parental education were subject to a large proportion of missing data ranging between 34% and 62%. For the other variables in Table 1 the degree of data completeness exceeded 90%. With the narrow age range in this study no association between odds of myopia and age was found. There were no significant differences in the proportion of girls and boys who were myopic. Number of younger siblings and physical activity were inversely associated with myopia, whereas attendance at a grammar school, and history of parental myopia were strongly positively associated with myopia. Although the univariate analyses showed a gradually increasing positive effect of the time spent on near vision activities and homework and the risk of myopia, this trend was not statistically significant.

In multiple variable adjusted regression analysis (Table 1) there is a significant trend between the levels of physical activity and the odds of myopia (p for trend = 0.027), with regular physical activity being associated with a lower prevalence of myopia as compared with sedentary lifestyles (OR=0.46, 95%CI 0.23 to 0.90). Children with younger siblings were less likely to be myopic (OR=0.77 per younger sibling, 95%CI 0.60 to 0.99). The odds of myopia was more than 2.5 times higher amongst children attending grammar schools (OR=2.66, 95%CI 1.48 to 4.78) compared to non-grammar schools. There was no evidence of an effect of urban versus non-urban environment on the odds of myopia.

Parental myopia is a strong risk factor for myopia; compared to children with no myopic parents, children with one myopic parent or both parents being myopic were 2.91 times (95%CI 1.54 to 5.52) and 7.79 times (95%CI 2.93 to 20.67) more likely to have myopia, respectively. In the model including parental myopia the trend for physical activity and the effect of type of schooling became marginally stronger; all other odds ratios were unchanged. However, due to the large amount of missing data in parental myopia, only 54.6% of all available records were used in this analysis which may have resulted in bias if, for example myopic parents were more likely to respond if their children were also myopic. However, we did not find any difference in response rates between parents of myopic or non-myopic children, those living in urban or rural settings or socio-economic position..

Excluding either economic deprivation or all non-significant variables from the multiple regression model in Table 1 made little difference to the odds ratios already presented for the other variables, except for attendance at a grammar school where the odds ratios for myopia became more marked (OR=2.97, 1.71 to 5.17; and OR=3.02, 1.87 to 4.90; respectively). We explored pairwise interactions between physical activity, number of younger siblings, type of schooling and parental myopia and did not find any statistically significant interactions (in all instances $p>0.1$)

Discussion

In this study based on school children of predominantly white European ancestry we have shown a strong relationship between estimated prevalence of myopia in children and history of parental myopia; a trend of decreasing prevalence of myopia with increasing levels of physical activity. However the cross sectional design of the study does not allow for causality to be determined and lower time spent in physical activity may reflect other issues related to poor distance vision. An increasing number of younger siblings seemed protective and grammar school attendance increased the risk of myopia. We did not find strong evidence of an association with age, sex, area level of deprivation, urbanicity, birth place, birth weight, childhood body size, intensity of near vision activities or level of parental education. Although associations with gender, and economic deprivation were not statistically significant, their effect on prevalence of myopia was in the expected direction,[6, 30] with girls being more likely to be myopic,[13, 15, 31-33] and those coming from less deprived economic backgrounds being at an increasingly higher risk.[13, 31, 32]

The lack of an association between urbanisation and myopia which has been reported in other studies[9] may be due to the current study's reliance on population density to assess urban/rural environments. Even in urban areas of Northern Ireland, population density remains lower than in many East Asian cities (http://www.metro.tokyo.jp/ENGLISH/PROFILE/overview03.htm, accessed 17th July 2014). Furthermore area measurements used to calculate population density figures for Northern Ireland are based on the official local government boundaries and include areas of inland water and estuaries. Population densities may therefore be artificially low in areas of close proximity to large bodies of water (Northern Ireland Statistics & Research Agency, 2005 *Statistical classification and delineation of settlements*, www.nisra.gov.uk/archive/demography/publications/urban_rural/ur_main.pdf, accessed 5th November 2008). Future analysis of the effect of urbanisation on myopia prevalence should use more detailed assessment of the level of urbanisation and include data on the type of housing and housing density.[9]

Greater time spent in near work activities showed some evidence of an increased risk of myopia but this relation was not statistically significant. Although other studies have shown near work is a risk factor for myopia the association is often weak[34] or inverse[35] and a consistent relationship has not been demonstrated.[35] Previous studies have also evaluated near work in a variety of ways including the use of diaries, child's performance on standardised reading scores,[36] calculation of dioptre hours (based on the reported number of hours spent on various near vision activities including reading, studying, computer use, video games),[3, 37] and the number of books read per week.[5] The method used can influence whether an association between near work and myopia is found; Saw *et al.* (2002) found no statistically significant association with myopia using the number of hours spent reading per week, but using the number of books read per week did show a statistically significant association despite the lack of information on the number of pages and the print size of the books read.[5] It is possible that the questionnaire-based method of establishing levels of near work used in the current study provided a relatively crude assessment of near work activity and perhaps not be sensitive enough, or the study may lack power, to fully establish any association between near work and myopia. Time outdoors, which was not assessed in the current study, has also been shown to reduce myopia in children who spend large amounts of time engaged in near work.[38] Furthermore recall bias is a potential problem and respondents may also inadvertently bias the results as many children and adults are aware of a possible link between near work and myopia which may influence their responses.

Mutti *et al.* (2002) suggested that it may be the inverse of near work (i.e. time spent in distance and outdoor activities) that may have a protective effect on the development of myopia.[4] Although outdoor activities were not assessed in the current study, the results do suggest that increased physical activity (implying more time spent outdoors) reduces the odds of myopia. Parental responses to questions regarding a child's sporting activity may be more accurate than those assessing near vision activity as many parents transport their children to and from sporting activities.[3] Further support for the association between myopia prevalence and lower levels of physical activity comes from studies that measured physical activity objectively using an accelerometer to avoid the inherent bias of subjective measures.[39-41] A recent systematic review suggested that increased time spent outdoors reduces the risk of myopia.[42]

The current study confirms previously reported associations between a parental history of myopia and myopia in childhood[4, 16, 43] and illustrates that the impact of parental myopia is dose-dependent. Although the reliability of self-reporting of refractive status history has been queried,[44] the questions used in the current study have been shown to be valid for assessing the presence of myopia.[45] The effect of parental myopia remained after adjustment for the other factors and points towards a genetic association. However, it is still possible that the association with parental myopia is, at least in part, due to shared environmental influence and that perhaps the tool we used to assess near vision was not sensitive Despite considerable missing data for this variable our estimates of effect for one or both parents being myopic agree very well with previous studies.[18, 46-48]

Grammar schooling appears to be a strong risk factor for myopia but this association is unlikely to be causal. Entrance to grammar schools in NI is a competitive academic process at age 11 years by which stage the children may have already developed myopia. Grammar schooling may be acting as a marker for increased level of education which has been shown to have an effect on the prevalence of myopia.[31, 49] Previous studies have suggested an association between intelligence and myopia.[26, 50, 51] Often these studies have relied on the use of IQ tests to determine intelligence and results are therefore dependent on the method used to assess IQ. In the current study IQ was not assessed directly hence it is not possible to evaluate whether the association between myopia and grammar school education is confounded by this marker of intelligence.

As with previous studies,[52] children from bigger families were less likely to be myopic. It may reflect the fact that in NI large family size is associated with poverty [Office of the First Minister and Deputy First Minister; http://www.ofmdfmni.gov.uk/childandfamilypoverty2006.pdf; date accessed 9th July

2014] and in the current study there was a trend for increasing deprivation to be associated with less myopia, although this was not statistically significant.

This study has examined the association between potential risk factors and presence of myopia at age 12-13-years and many of the reported associations support previous findings, notwithstanding that some lacked power to reach statistical significance. The children in this study are being reassessed at three yearly intervals and further review will help confirm whether these environmental influences are indeed prospective risk factors for myopia.

Conclusion

In Northern Ireland children parental history of myopia and type of schooling, are important determinants of myopia. at age 12-13-years. Further work is underway to assess whether this remains the most significant indicator of refractive outcome or whether environmental factors become more influential on the likelihood of being myopic with increasing age.

Acknowledgements

The authors would like to thank the College of Optometrists, UK for their ongoing support for the NICER study. We are also very grateful to the participants in the NICER study for their ongoing commitment to this research and to the schools where the research is conducted.

Table 1: Unadjusted† and adjusted‡ odds ratios of myopia for socio-demographic and life style risk factors

Risk factor	n/N	(%)	Unadjusted odds ratio† (95% CI)	p-value	p-value for heterogeneity (trend)	n/N	(%)	Adjusted odds ratio‡ (95% CI)	p-value	p-value for heterogeneity (trend)
Demographics										
Age per year (Mean ± SD = 13.1 ± 0.4)	117/661	(18%)	1.71 (0.89, 3.27)	0.11		106/587	(18%)	1.09 (0.55, 2.15)	0.80	
Gender										
Boys	52/334	(16%)	1.00			49/303	(16%)	1.00		
Girls	65/327	(20%)	1.44 (0.93, 2.25)	0.11		57/284	(20%)	1.32 (0.83, 2.09)	0.24	
Family size (mutually adjusted)										
Per younger siblings	106/610	(17%)	0.75 (0.59, 0.95)	0.020	0.065	106/587	(18%)	0.77 (0.60, 0.99)	0.038	0.11
Per older siblings	106/610	(17%)	0.92 (0.76, 1.11)	0.38		106/587	(18%)	0.95 (0.79, 1.16)	0.64	
Type of Schooling										
Non-grammar school	45/374	(12%)	1.00			34/303	(11%)	1.00		
Grammar school	72/287	(25%)	2.45 (1.62, 3.69)	<0.001		72/284	(25%)	2.66 (1.48, 4.78)	0.001	
Deprivation score										
1st quintile (most deprived)	15/130	(12%)	1.00			14/130	(11%)	1.00		
2nd quintile	16/130	(12%)	1.06 (0.49, 2.27)	0.89		15/130	(12%)	1.01 (0.44, 2.32)	0.98	
3rd quintile	34/130	(26%)	2.52 (1.24, 5.11)	0.010	0.055 (0.17)	30/130	(23%)	1.57 (0.72, 3.43)	0.26	0.72 (0.70)
4th quintile	24/130	(18%)	1.61 (0.77, 3.38)	0.21		23/130	(18%)	1.13 (0.50, 2.55)	0.77	
5th quintile (least deprived)	26/130	(20%)	1.74 (0.82, 3.70)	0.15		24/130	(18%)	1.22 (0.55, 2.70)	0.62	
Living environment										
Not urban	71/367	(19%)	1.00			66/337	(20%)	1.00		
Urban	45/287	(16%)	0.83 (0.54, 1.29)	0.41		40/250	(16%)	0.91 (0.55, 1.48)	0.70	
Birth place										
Not NI	7/31	(23%)	1.00							
NI	68/403	(17%)	0.66 (0.27, 1.63)	0.37						

Risk factor	n/N	(%)	Unadjusted odds ratio† (95% CI)	p-value	p-value for heterogeneity (trend)	n/N	(%)	Adjusted odds ratio‡ (95% CI)	p-value	p-value for heterogeneity (trend)
Activities										
Physical activity (per week)										
Sedentary	23/113	(20%)	1.00			22/108	(20%)	1.00		
Light physical activities	27/147	(18%)	0.74 (0.38, 1.42)	0.36	0.13 (0.037)	27/145	(19%)	0.70 (0.36, 1.36)	0.30	0.13 (0.027)
Regular sporting act (up to 3hr)	27/127	(21%)	0.83 (0.43, 1.62)	0.58		27/123	(22%)	0.77 (0.38, 1.54)	0.46	
Regular sporting act (more than 3hr)	30/212	(14%)	0.48 (0.25, 0.93)	0.030		30/211	(14%)	0.46 (0.23, 0.90)	0.024	
Near vision time										
Most time close work	16/84	(19%)	1.00							
Frequent close work	32/152	(21%)	0.97 (0.48, 1.95)	0.92	0.46 (0.12)					
Occasional close work	38/208	(18%)	0.81 (0.41, 1.60)	0.54						
Little close work	21/161	(13%)	0.62 (0.30, 1.27)	0.19						
Homework time (per day)										
None	1/21	(5%)	1.00							
Less than 1 hr	50/305	(16%)	3.37 (0.43, 26.19)	0.25	0.66 (0.19)					
1-2 hrs	47/250	(19%)	3.78 (0.48, 29.72)	0.21						
2-3 hrs	7/30	(23%)	4.53 (0.49, 41.67)	0.18						
More than 3 hrs	2/7	(29%)	6.38 (0.46, 89.01)	0.17						
Child factors										
Birth weight (Mean ± SD = 3.5 ± 0.6Kg)	70/410	(17%)	1.31 (0.81, 2.12)	0.27						
BMI (Mean ± SD = 20.8 ± 3.7 Kg/m²)	117/660	(18%)	0.98 (0.92, 1.04)	0.42						
BMI group (IOTF)										
Normal weight	83/480	(17%)	1.00							
Overweight	30/147	(20%)	1.27 (0.79, 2.05)	0.32	0.51 (0.72)					
Obese	4/33	(12%)	0.76 (0.25, 2.30)	0.63						

Risk factor	n/N	(%)	Unadjusted odds ratio† (95% CI)	p-value	p-value for heterogeneity (trend)	n/N	(%)	Adjusted odds ratio‡ (95% CI)	p-value	p-value for heterogeneity (trend)
Parental factors										
Parental myopia										
None	25/227	(11%)	1.00			25/225	(11%)	1.00		
One parent	28/109	(26%)	2.79 (1.54, 5.08)	0.001	<0.001 (<0.001)	28/109	(26%)	2.91 (1.54, 5.52)#	0.001	<0.001 (<0.001)
Both parents	12/27	(44%)	6.46 (2.72, 15.36)	<0.001		12/27	(44%)	7.79 (2.93, 20.67)#	<0.001	
Parental education										
Low	17/113	(15%)	1.00							
Medium	17/98	(17%)	1.19 (0.57, 2.47)	0.65	0.83 (0.56)					
High	22/123	(18%)	1.23 (0.62, 2.46)	0.56						

n = number of cases of myopia per number of children with available data (N).

† Odds ratios are not mutually adjusted but take into account the clustering of children within schools

‡ Odds ratios are mutually adjusted for all factors listed in the column of adjusted odds ratios except for parental myopia, and adjusted for the clustering of children within schools.

Odds ratios are obtained from a separate model fitted to a subset of the data, adjusting for age, gender, family size, school, deprivation score, living environment, physical activity and for the clustering of children within schools.

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