

# Early life factors for myopia in the British Twins Early Development Study

Katie M Williams,<sup>1,2</sup> Eva Kraphol,<sup>3</sup> Ekaterina Yonova-Doing,<sup>2</sup> Pirro G Hysi,<sup>1,2</sup> Robert Plomin,<sup>3</sup> Christopher J Hammond<sup>1,2</sup>

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<sup>1</sup>Section of Academic Ophthalmology, School of Life Course Sciences, FoLSM, King's College London, London, UK

<sup>2</sup>Department of Twin Research & Genetic Epidemiology, School of Life Course Sciences, FoLSM, King's College London, London, UK

<sup>3</sup>MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

## Correspondence to

Dr Christopher J Hammond, Section of Academic Ophthalmology, School of Life Course Sciences, FoLSM, King's College London, London WC2R 2LS, UK; [chris.hammond@kcl.ac.uk](mailto:chris.hammond@kcl.ac.uk)

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## ABSTRACT

**Purpose** Myopia is an increasingly prevalent condition globally. A greater understanding of contemporaneous, early life factors associated with myopia risk is urgently required, particularly in younger onset myopia as this correlates with higher severity and increased complications in adult life.

**Methods** Analysis of a subset of the longitudinal, UK-based Twins Early Development Study (n=1991) recruited at birth between 1994 and 1996. Subjective refraction was obtained from the twin's optometrists; mean age 16.3 years (SD 1.7). Myopia was defined as mean spherical equivalent  $\leq -0.75$  dioptres. A life course epidemiology approach was used to appropriately weight candidate myopia risk factors during critical periods of eye growth. Adjusted ORs for myopia were estimated using multivariable logistic regression models at each life stage, together with variance explained ( $r^2$ ) and area under the receiver operator characteristic curve (AUROC) statistic of predictive models.

**Results** Factors significantly associated with myopia included level of maternal education (OR 1.33, 95% CI 1.11 to 1.59), fertility treatment (OR 0.63, 95% CI 0.43 to 0.92), summer birth (OR 1.93, 95% CI 1.28 to 2.90) and hours spent playing computer games (OR 1.03, 95% CI 1.01 to 1.06). The total variance explained by this model was 4.4% ( $p < 0.001$ ) and the AUROC was 0.68 (95% CI 0.64 to 0.72). Consistent associations were observed with socioeconomic status, educational attainment, reading enjoyment and cognitive variables, particularly verbal cognition, at multiple points over the life course.

**Conclusions** This study identifies known and novel associations with myopia during childhood development; associated factors identified in early life reflect sociological and lifestyle trends such as rates of maternal education, fertility treatment, early schooling and computer games.

Myopia, or near-sightedness, occurs when there is axial elongation of the eye in childhood resulting in a focused image forming in front of the retinal plane. This requires refractive correction but continues to place an individual at an increased risk of potentially sight-threatening diseases.<sup>1</sup> The prevalence of myopia has increased worldwide, most dramatically in urban Asia.<sup>2</sup> There is increasing interest in strategies to reduce the development and progression of myopia during childhood.

Before the age of 2 years, there is rapid eye growth,<sup>3</sup> correlating with the reduction of the typical hyperopia of infancy (emmetropisation).

Scleral remodelling allows axial growth of the eye to near-adult size by the age of 10 years.<sup>4</sup> Early visual experience is highly influential in eye growth and refractive development.<sup>5</sup> Future myopic status can be predicted by refraction in childhood,<sup>6</sup> while early onset myopia is associated with higher myopia in adulthood and a greater risk of ocular complications.

Although genetic inheritance is a key determinant of myopia,<sup>7</sup> genetic factors alone cannot explain the rising prevalence. Given the rapid ocular growth in early life, this study analysed various candidate myopia risk factors using a life course epidemiology approach. This enables appreciation for risk accumulation over childhood development, identification of processes operating across different life stages and consideration of exposures during critical periods of development and ocular growth.

## MATERIALS AND METHODS

### Study population

The Twins Early Development Study (TEDS) is a longitudinal, twin birth cohort, studied using multivariate quantitative and molecular genetic methods with a specific focus on neurodevelopment, cognition, behaviour and education. Twins born between 1994 and 1996 from England and Wales were recruited and despite some attrition the sample remains representative of the UK population for this generation.<sup>8</sup> For this TEDS myopia study, a subset of 2625 families were selected, prioritising twins with genotype data and actively participating. Exclusions included severe medical problems and families who were not contactable. The research adheres to the tenets of the Declaration of Helsinki.

### Study variables

Postal questionnaires were sent to the families in the TEDS myopia study, and informed consent to contact the twins' optician for a recent refraction was sought from both the parents and the twins. A response rate of 51.7% from potential families (n=1359) was obtained; this comprised 2715 twin participants. Non-responders and responders were similar in terms of ethnicity, gender, zygosity, age and parental employment. Among responders, there was a higher level of school achievement: 90% of responders achieved higher grades (A\* to C) in secondary school compared with 84% in non-responders. Questionnaires were posted to the optometrists of the 2283 twin participants who had undergone an eye test and provided consent. Non-cycloplegic, subjective refractive



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error measurements were obtained for 1991 individuals. Spherical equivalent (SE) was calculated using the standard formula ( $SE = \text{sphere} + (\text{cylinder}/2)$ ), and the mean of the two eyes was considered. Myopia was defined as  $SE \leq -0.75$  dioptres (D) with low myopia:  $\leq -0.75$  to  $> -3$ D, moderate myopia:  $\leq -3$  to  $> -6$ D and high myopia:  $\leq -6$ D.

The twins, parents and school teachers have completed extensive questionnaires over early life, in addition to web-based testing and home assessments. We examined potential myopia risk factors at ages 2, 3, 4, 7, 8, 10, 12, 14 and 16 years. Particular attention was placed on cognitive, behavioural and educational variables, together with extracurricular interests, namely time outside and near-work activities. Photoperiod was calculated by downloading 'civil twilight' hours in 1995 from a public repository.<sup>9</sup>

### Statistical analysis

Candidate myopia risk factors were evaluated using a life course approach with five life stages: preconception; prenatal, perinatal and postnatal; preschool ( $\leq 4$  years); childhood ( $\leq 11$  years); and adolescence ( $\leq 18$  years). Univariable and multivariable logistic regression models for risk of adolescent myopia ( $\leq -0.75$ D vs  $> -0.75$ D) at each life stage were constructed, with clustering to adjust for family relatedness. In the scenario of multiple classes of dependent variables, a test for trend was used to compare ORs. At each life stage, the multivariable model incorporated adjustment for age at refraction, sex and factors significantly associated with myopia at any earlier life stage ( $p < 0.05$  in the multivariable model). At the adolescence life stage, myopic status was restricted to those who underwent an eye examination after the age of 14 years to avoid assessment of candidate risk factors subsequent to refractive error measurement. The linear variance explained ( $r^2$ ) and area under the receiver operator characteristic curve (AUROC) statistic of the final logistic predictive model was calculated, with adjustment for multiple testing using Bonferroni correction and cross-validation. Analysis was performed using Stata V.13.1.

## RESULTS

SE was calculated on 1991 twin participants with a median age at refraction of 16.7 years (range 5.7–18.8 years, SD 1.75, 92% aged 14–18 years). The mean SE was  $-0.35$ D (SD 1.80). The mean age at which myopic glasses were first worn was 11.0 years (SD 3.8). Amblyopia was reported in 5.4%, and 4.3% had a documented squint. Overall 25.9% of the cohort was myopic (95% CI 24.0 to 27.8).

### Preconception

Maternal and paternal highest educational level (scale of 1–8 from no qualification to postgraduate qualification) achieved were significantly associated with myopia in the twins (table 1): myopia OR 1.59 (95% CI 1.00 to 2.51) with a university-educated father and OR 2.15 (95% CI 1.09 to 4.25) with a mother who achieved likewise. In multivariable analyses, only maternal educational attainment remained significant (OR 1.31, 95% CI 1.16 to 1.55). Parental educational levels were correlated ( $r = 0.43$ ,  $p < 0.01$ ), but sensitivity analyses did not affect results. In univariable analyses, there was a significant trend for increased myopia with a 'stay-at-home' father (OR 1.91) and increasing social class defined by the father's occupation (OR 1.14).

### Prenatal, perinatal and postnatal

Fertility treatment was significantly associated with reduced odds of myopia in multivariable analysis (0.75, 95% CI 0.57 to 1.0) (table 1). Fertility treatment was moderately correlated with maternal age ( $r = 0.30$ ,  $p < 0.01$ ), minimally correlated with maternal education ( $r = 0.05$ ,  $p < 0.01$ ) and inversely correlated with both gestational age ( $-0.04$ ,  $p < 0.01$ ) and birth weight ( $-0.04$ ,  $p < 0.01$ ). When adjusted for all of these correlates, the association between fertility treatment and myopia strengthened (OR 0.63, 95% CI 0.41 to 0.98). We explored the association between seasons of birth defined by academic terms and detected a significant increase in risk across successive terms in multivariable analysis: those born in the 'summer term' had the highest odds of myopia (OR 1.50, 95% CI 1.11–2.05). There was no significant association with photoperiod or mediation by birth weight. Those of non-white British ethnicity had nearly double the odds of myopia (OR 1.85, 95% CI 1.11–3.09) in univariable analysis; ethnicity subclassification was not possible, although numbers of non-white ethnicity were small ( $n = 85$ ). We did not replicate the association between myopia and maternal smoking.<sup>10</sup>

### Preschool

A large number of potential risk factors at this life stage were explored given this is a critical period for eye growth, but only eyesight problems at age three were significantly associated (adjusted OR 0.23, 95% CI 0.09 to 0.6) (online supplementary file 1). This probably reflects children with significant hyperopia, who are unlikely to become myopic; their mean SE in adolescence was  $+1.96$ D.

### Childhood

Significant associations for increased odds of adolescent myopia were current maternal qualifications (OR 1.10) and a non-working father (OR 2.01) at the age of 7 years (online supplementary file 2). Verbal cognitive ability (aged 10 years) was associated with myopia (OR 1.29, 95% CI 1.08 to 1.55), as was composite cognitive ability (g) (OR 1.22, 95% CI 1.01 to 1.47). None of the factors were significant in the multivariable model.

### Adolescence

Myopia in late adolescence was associated with verbal cognition at age 12 years (OR 1.22, 95% CI 1.06 to 1.40) and age 14 years (OR 1.04, 95% CI 1.01 to 1.07). At age 16 years, myopia was associated with composite 'g' (OR 1.30, 95% CI 1.12 to 1.49), verbal (OR 1.06, 95% CI 1.03 to 1.10) and non-verbal cognition (OR 1.04, 95% CI 1.01 to 1.08). No cognitive variable was significant in the multivariable model (table 2). Hours spent on computer games per week were significantly associated in multivariable analyses (OR 1.06, 95% CI 1.02 to 1.10). Hours spent reading showed a trend towards increased odds of myopia while reading enjoyment rating was significant in univariable analysis (OR 1.14, 95% CI 1.04 to 1.26). Number of higher grades (OR 1.05, 95% CI 1.00 to 1.10) and 'total points' (OR 1.01, 95% CI 1.00 to 1.01) achieved in examinations undertaken at age 16 years were associated in univariable analyses.

Significant factors in multivariable analysis at each life stage were combined into one single model in 1077 individuals, with adjustment for age and sex (figure 1). The following factors remained significant: maternal education (OR 1.33, 95% CI 1.11 to 1.59), fertility treatment (OR 0.63, 95% CI 0.43 to 0.92), summer birth (1.93, 95% CI 1.28 to 2.90) and hours spent playing computer games (OR 1.03, 95% CI 1.01 to 1.06). Using a linear fit model with the continuous trait of SE, the total

**Table 1** Preconception factors and prenatal, perinatal and postnatal factors

Potential risk factor	Myopia ( $\leq -0.75D$ )				
	Unadjusted model			Adjusted model	
	n	OR (95% CI)†	P values	OR (95% CI)‡ (n=1776)	P values/p trend
<b>Preconception factors</b>					
Maternal education	1991	1.32 (1.16 to 1.50)	<0.001*	1.31 (1.11 to 1.55)	0.001*
Secondary school exams aged 16 years (GCSEs)	94	1.00		1.00	
Secondary school exams aged 18 years (A Levels)/vocational certificate or diploma	448	2.14 (1.08 to 4.27)		2.40 (0.97–5.95) 2.08 (0.84–5.18)	0.025*
University degree	536	2.15 (1.09 to 4.25)	<0.001*		
Paternal education	1991	1.15 (1.02 to 1.30)	0.026*	0.99 (0.83 to 1.17)	0.883
No qualification	169	1.00		1.00	
Secondary school exams aged 16 years (GCSEs)	674	1.22 (0.75 to 1.98)		1.08 (0.62 to 1.90)	0.920
Secondary school exams aged 18 (A Levels)/vocational certificate or diploma	480	1.22 (0.75 to 1.98)		0.87 (0.48 to 1.58)	
University degree	668	1.59 (1.00 to 2.51)	0.008*		
Maternal job	1978	1.00			
Working	959	1.00			
Staying at home with children	844	0.93 (0.72 to 1.20)	0.411		
Not working	175	0.88 (0.57 to 1.36)			
Paternal job	1888				
Working	1801	1.00			
Staying at home with children	28	1.91 (0.70 to 5.23)			
Not working	59	1.63 (0.88 to 3.01)	0.028*	collinearity	
Higher maternal socioeconomic status based on employment	945	1.13 (0.95 to 1.34)	0.162		
Higher paternal socioeconomic status based on employment	1781	1.14 (1.04 to 1.26)	0.005*	1.06 (0.94 to 1.18)	0.362
<b>Prenatal, perinatal and postnatal factors</b>					
Smoking during pregnancy (cigarettes/day)	1965	0.87 (0.66 to 1.17)	0.380		
Alcohol during pregnancy (units/week)	1931	0.98 (0.81 to 1.18)	0.834		
Age of mother (years)	1964	1.01 (0.98 to 1.03)	0.610		
Fertility treatment	1982				
No	1442	1.00		1.00	
Yes	540	0.71 (0.54 to 0.94)*	0.017*	0.75 (0.57 to 1.00)	0.047*
Gestational age at birth (weeks)	1952	0.98 (0.93 to 1.02)	0.349		
Ethnic group of twin	1989				
White British	1904	1.00	0.018*	1.00	0.120
Other	85	1.85 (1.11 to 3.09)*	0.018*	1.52 (0.90 to 2.58)	
Gender	1991				
Female	1156	1.00			
Male	835	0.88 (0.70 to 1.11)	0.273		
Birth weight (adjusted for gestational age and gender, grams)	1953	1.00 (1.00 to 1.00)	0.962		
Length at birth (adjusted for gestational age and gender, centimetres)	989	1.01 (0.97 to 1.06)	0.593		
Photoperiod at birth (increasing daylight hours)		1.07 (0.96 to 1.19)			
1	611	1.00			
2	475	0.91 (0.65 to 1.27)	0.237		
3	450	1.03 (0.74 to 1.44)			
4	455	1.21 (0.87 to 1.68)			
1–4			0.149		
Season (by academic term) of birth	1991	1.18 (1.02 to 1.37)	0.024*	1.22 (1.05 to 1.43)	0.011*
Autumn (September–December)	772	1.00		1.00	0.011*
Spring (January–April)	625	1.19 (0.89 to 1.58)	0.024*	1.08 (0.80 to 1.46)	0.007*
Summer (May–August)	594	1.40 (1.05 to 1.89)	0.006*	1.50 (1.11 to 2.05)	0.007*

Continued

Table 1 Continued

Potential risk factor	Myopia ( $\leq -0.75D$ )				
	Unadjusted model			Adjusted model	
	n	OR (95% CI)†	P values	OR (95% CI)‡ (n=1776)	P values/p trend
Breast fed (y/n)	1944	1.04 (0.80 to 1.35)	0.784		
Regular sleeping pattern (y/n)	1945	0.95 (0.82 to 1.10)	0.478		
Length of stay in special care baby unit after birth (days)	736	1.00 (0.98 to 1.01)	0.572		
Length of stay in hospital after birth (days)	1932	1.00 (0.99 to 1.01)	0.993		

\*P<0.05; \*\*p<0.10.

†Adjusted for family relatedness.

‡Adjusted for age at refraction, sex, family relatedness and significant factors in univariable analyses.

A Levels, advanced level (secondary school higher exams taken at the age of 18+ years in the UK). Highly correlated variables not included in multivariable model as collinearity exclusion; GCSEs, General Certificate of Secondary Education (secondary school exams taken at the age of 16 years in the UK).

variance explained was 4.4% ( $p < 0.001$ ), with a baseline model of age and sex contributing 1.6%. The AUROC was 0.68 (95% CI 0.64 to 0.72) (figure 2). A k-fold cross validation produced a comparable AUROC of 0.67 (95% CI 0.63 to 0.70).

## DISCUSSION

We attempted to address the question of what early life factors in modern-day childhood contribute to myopia and identified

maternal education, playing computer games and a summer birth to be associated with increased odds, while fertility treatment appeared protective. Suggestive associations across childhood were found with higher socioeconomic status and cognitive scores (akin to intelligence), in particular verbal cognition. In addition to novel findings, we confirm the findings of a previous life course study (1958 British Birth Cohort<sup>10</sup> that factors in early childhood influence ocular growth trajectories.

Table 2 Adolescence factors

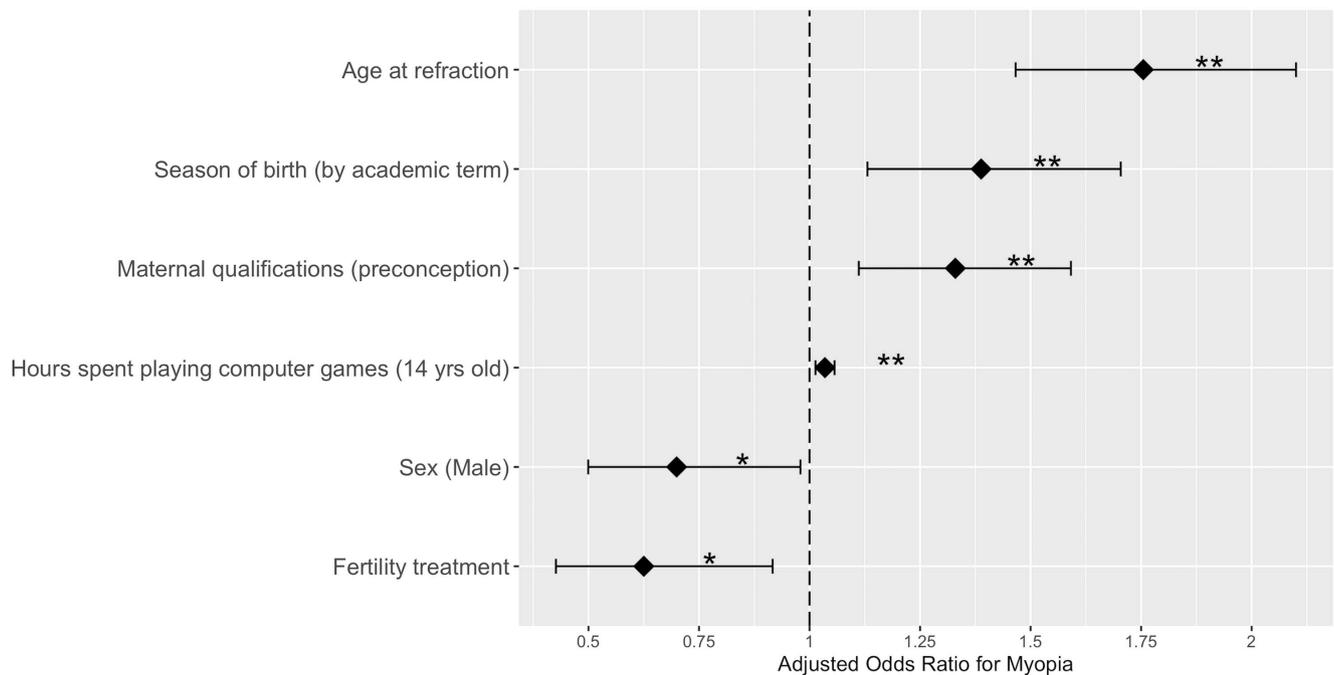
Potential risk factor	Myopia ( $\leq -0.75D$ )				
	Unadjusted model			Adjusted model	
	n	OR (95% CI)†	P Values	OR (95% CI)‡ (n=449)	P values/p trend
Age 12 Cognitive ability (g) (standardised scale)	1489	1.11 (0.96 to 1.27)	0.148		
Age 12 Verbal cognitive ability (standardised scale)	1512	1.22 (1.06 to 1.40)	0.005*	0.72 (0.48 to 1.08)	0.112
Age 12 Non-verbal cognitive ability (standardised scale)	1489	0.98 (0.86 to 1.12)	0.756		
Age 12 Conners inattention scale (0–27)	1259	1.01 (0.98 to 1.03)	0.664		
Age 14 Physical sports (hours/week)	1147	0.98 (0.95 to 1.01)	0.175		
Age 14 Computer games (hours/week)	1086	1.02 (1.00 to 1.04)	0.015*	1.06 (1.02 to 1.10)	0.003*
Age 14 Watching TV (hours/week)	1126	1.00 (0.99 to 1.02)	0.749		
Age 14 Outside with friends (hours/week)	1049	1.00 (0.97 to 1.02)	0.824		
Age 14 Reading (hours/week)	1060	1.01 (0.99 to 1.04)	0.206		
Age 14 Reading (increasing rating of enjoyment 1–6)	1206	1.14 (1.04 to 1.26)	0.006*	1.21 (0.97 to 1.51)	0.091**
Age 14 English teacher assessment (scale 1–8)	1039	1.08 (0.92 to 1.26)	0.342		
Age 14 Maths teacher assessment (scale 1–8)	1047	1.10 (0.95 to 1.26)	0.196		
Age 14 Science teacher assessment NC (scale 1–8)	1040	1.07 (0.91 to 1.25)	0.422		
Age 14 Cognitive ability (g) (standardised scale)	882	1.16 (0.97 to 1.38)	0.097**		
Age 14 Ravens web test (non-verbal) (standardised scale)	895	1.02 (0.97 to 1.06)	0.448		
Age 14 Vocabulary web test (scale 0–53)	1055	1.04 (1.01 to 1.07)	0.023*	1.02 (0.95 to 1.08)	0.619
Age 16 Household income category (0–12, both parents)	1040	1.04 (0.97 to 1.10)	0.269		
Age 16 Father highest qualification level (scale 1–8)	1133	1.02 (0.99 to 1.04)	0.273		
Age 16 Father socioeconomic level (scale 1–9)	1011	1.06 (0.99 to 1.14)	0.090**		
Age 16 Mother highest qualification level (scale 1–8)	1220	1.10 (1.02 to 1.18)	0.012*	0.80 (0.63 to 1.01)	0.058†
Age 16 Mother socioeconomic level (scale 1–9)	1050	1.07 (0.99 to 1.16)	0.071**		
Age 16 No. of GCSEs passes at grades A* to C	1747	1.05 (1.00 to 1.10)	0.045*	Collinearity	
Age 16 Total point score for GCSEs	1747	1.01 (1.00 to 1.01)	0.002*	1.01 (0.99 to 1.02)	0.427
Age 16 Cognitive ability (g) (standardised scale)	1067	1.30 (1.12 to 1.49)	<0.001*	1.23 (0.92 to 1.64)	0.155
Age 16 Ravens web test (non-verbal, scale 0–30)	1094	1.04 (1.01 to 1.08)	0.018*	Collinearity	
Age 16 Mill Hill vocabulary web test (scale 0–33)	1155	1.06 (1.03 to 1.10)	<0.001*	Collinearity	
Age 16 Height (cm)	980	0.98 (0.96 to 0.99)	0.010*	0.97 (0.94 to 1.01)	0.176
Age 16 Weight (kg)	980	0.99 (0.98 to 1.01)	0.275		

\*P<0.05, \*\*p<0.10.

†Adjusted for family relatedness.

‡Adjusted for age at refraction, sex, family relatedness, significant factors in univariable analyses & factors significant in adjusted analyses at any earlier life stages.

GCSEs, General Certificate of Secondary Education (secondary school exams taken at the age of 16 years in the UK).

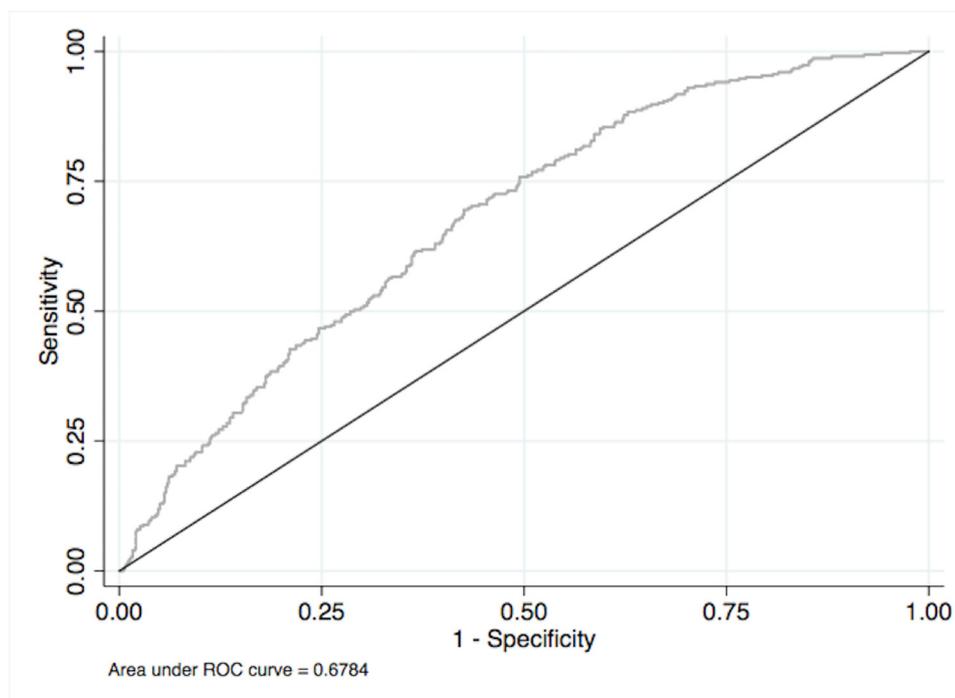


**Figure 1** Predictors for myopia from the life course analysis (adjusted OR for myopia with 95% CI). \*Significant factors; \*\*Significant factors after Bonferroni correction.

We replicate a consistent association between maternal education and myopia in her offspring.<sup>11</sup> This probably reflects several (mutually inclusive) influences including parenting style, socioeconomic status, wealth, educational encouragement and potentially shared genetic factors. Notably in a life course analysis, under the assumption that certain traits remain stable, the same association is tested repeatedly at multiple life stages providing a more robust estimate. Therefore, the association between

maternal education and myopia, which was replicated at multiple stages, has a greater credibility.

Fertility treatment was inversely associated with myopia—a novel finding that requires replication. Contrary to expectation that women undergoing fertility treatment have more myopia risk factors (higher educational status and subsequently older; higher socioeconomic status and therefore able to afford treatment), we observed a 25%–30% reduction in myopia odds,



**Figure 2** Receiver operating characteristic curves for prediction of myopia. AUROC, area under the receiver operator characteristic curve.

despite adjustment for possible confounders. This could, in part, be related to the fact that infants born following fertility treatment tend to have a lower birth weight and shorter gestation<sup>12</sup> and have, in some but not all studies, developmental delay and reduced cognitive scores.<sup>13</sup> A further potential factor that requires greater research is the potential effect of DNA methylation variation in children conceived by fertility treatment, a link that has explored in other phenotypes.<sup>14</sup>

In the UK, children start school in the September of the academic year in which they turn 5 years. Therefore, those born in the summer could be almost a whole calendar year younger than those born in autumn. In this study, children entering the educational system at a younger age (born in the summer months) had the highest odds of myopia. Previous studies of Finnish, Israeli, British and American populations also identified increased myopia with summer births, with several studies attributing this to increased natural light exposure during the postnatal period.<sup>9</sup> We find no association with light levels at birth and propose the association may be attributable to early exposure to the educational system. Season of birth has long-lasting associations with educational outcomes,<sup>15 16</sup> and axial elongation accelerates on starting school.<sup>17</sup> The importance of age of school entry presents an interesting topic for further research with potential implications for public health policy.

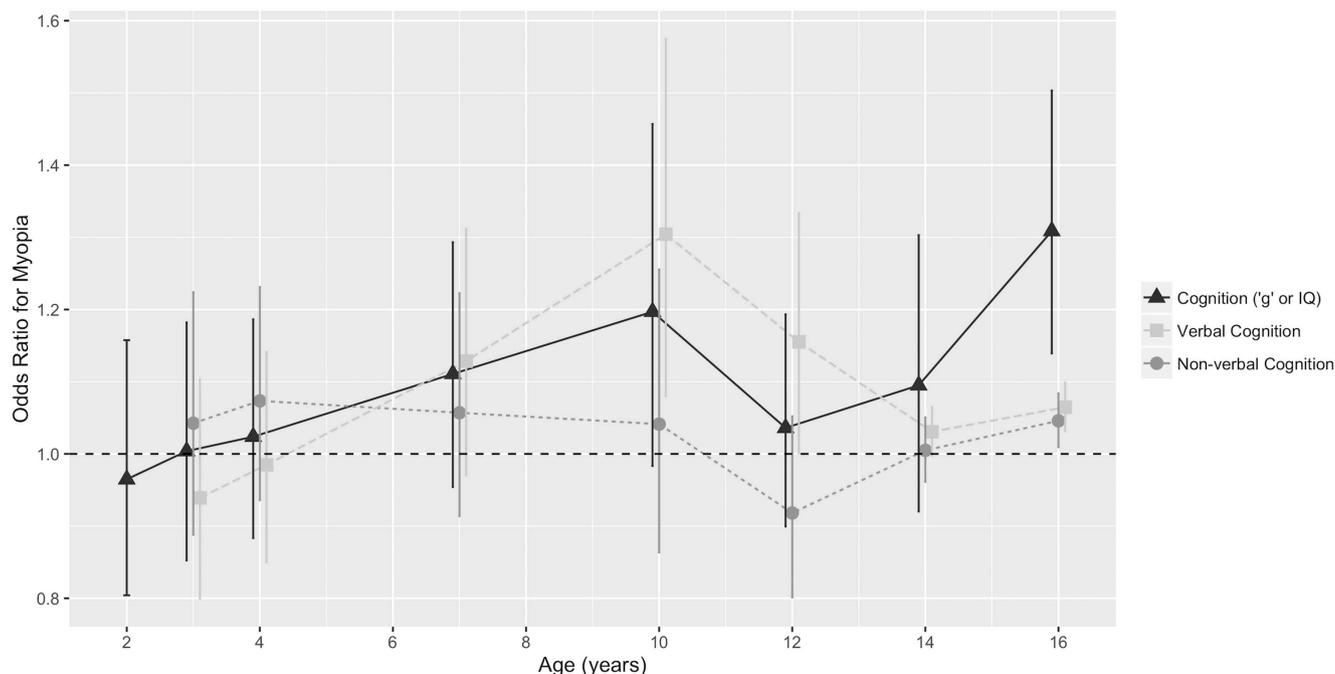
Hours spent playing computer games in early adolescence increased the odds of being myopic. The twins answered this question around 2008 (predating hand-held tablets) when most computer consoles were played indoors on television screens (eg, *PlayStation2* and *X-Box*). This association has previously been reported when included in a total of 'near-work hours',<sup>18</sup> while time spent gaming was identified to be different between myopes and emmetropes when measured after myopia onset but not before.<sup>19</sup> We did not replicate the protective effects of time outdoors,<sup>20</sup> but this variable was not carefully measured in this cohort. We found an association with reading enjoyment in univariable analyses. The 'liking' of reading has previously

shown to be correlated with myopia.<sup>21</sup> We suggest this trait and the association with computer games may not simply reflect time spent on near-work activity but something in the broader behaviour of those children, as others have suggested,<sup>22</sup> or less time outdoors.

Intelligence and educational achievement are established myopia risk factors.<sup>21 23</sup> Over the life course, verbal cognition and overall cognitive ability were associated with myopia. Generally associations were not statistically significant at early ages, possibly reflecting the difficulty in measuring these parameters in young children, and not retained in multivariable models, perhaps due to their correlation with maternal education. However, there is a clear trend in association over childhood (figure 3), with verbal cognition showing a higher level of association than non-verbal.

The age of myopia onset (11 years), as defined by the start of glasses wear, was comparable with similar cohorts<sup>24</sup> and notably younger than historical UK studies.<sup>10</sup> A life course multivariable risk factor model explained ~4% of refractive error variance. This is comparable with previous estimates of 2%–12%.<sup>18 23</sup> Predictive models have been tested in longitudinal studies,<sup>6 25 26</sup> with AUC statistics between 0.82 and 0.93. The AUROC in our study was 0.68, despite a lack of data on ocular biometry and parental myopia as used in other studies.

Although the TEDS study remains population representative,<sup>8</sup> the subsample invited, together with the 52% response rate, means those in the myopia study may not be. Higher educational status of responders may confer higher myopia prevalence. Missing data may affect power to detect associations: numerous potential determinants of myopia were explored and refractive error was only available on a subset. The myopia study was not initiated at the start of TEDS; therefore, questionnaires were not designed to target myopia risk factors. As the oldest participants were 18 years, misclassification of adult myopic status may have occurred; however, this methodology is likely to have captured all of the more highly myopic individuals, who are of most



**Figure 3** Association between myopia, overall cognition, verbal cognition and non-verbal cognition over the life course (adjusted OR for myopia with 95% CI).

clinical interest. Subjective, non-cycloplegic refractions by practising optometrists were used. At age 14–18 years, the subjects were old enough for subjective refraction with techniques to avoid excessive diagnosis of myopia. In adult epidemiological studies, this method introduces minimal bias; in younger populations, it has been found that while there is a large degree of inaccuracy in children <10 years, in older teenagers, inaccuracy is less, particularly with subjective rather than autorefraction.<sup>27</sup> In order to reduce overclassification of myopia, we used a definition of  $\leq -0.75D$  (as opposed to  $\leq -0.5D$ , commonly used in paediatric studies). Finally, these analyses identify associations but do not imply a causal direction; correlations between various early life factors and myopia could be mediated by a latent factor, such as genetics.

In conclusion this study of a contemporaneous, birth cohort highlights maternal education, early schooling and hours playing computer games as key predictors of myopia as a child enters adulthood. Fertility treatment appeared to reduce myopia risk. Socioeconomic factors, educational attainment and cognitive variables were related to myopia at multiple points over the life course. Given the rise in myopia prevalence, likely due to changing environmental pressures in childhood, further studies of this and other cohorts are warranted, in conjunction with genetic data, to continue efforts to produce predictive models that can ascertain who should be targeted for treatments to reduce the future burden of this condition.

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## REFERENCES

- 1 Flitcroft DJ. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res* 2012;31:622–60.
- 2 Dolgin E. The myopia boom. *Nature* 2015;519:276–8.
- 3 Larsen JS. The sagittal growth of the eye. IV. Ultrasonic measurement of the axial length of the eye from birth to puberty. *Acta Ophthalmol* 1971;49:873–86.
- 4 Harper AR, Summers JA. The dynamic sclera: extracellular matrix remodeling in normal ocular growth and myopia development. *Exp Eye Res* 2015;133:100–11.
- 5 Stone RA, Lin T, Desai D, et al. Photoperiod, early post-natal eye growth, and visual deprivation. *Vision Res* 1995;35:1195–202.
- 6 Zadnik K, Sinnott LT, Cotter SA, et al. Prediction of juvenile-onset myopia. *JAMA Ophthalmol* 2015;133:683–9.
- 7 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.
- 8 Haworth CM, Davis OS, Plomin R. Twins Early Development Study (TEDS): a genetically sensitive investigation of cognitive and behavioral development from childhood to young adulthood. *Twin Res Hum Genet* 2013;16:117–25.
- 9 McMahon G, Zayats T, Chen YP, et al. Season of birth, daylight hours at birth, and high myopia. *Ophthalmology* 2009;116:468–73.
- 10 Rahi JS, Cumberland PM, Peckham CS. Myopia over the lifecourse: prevalence and early life influences in the 1958 British birth cohort. *Ophthalmology* 2011;118:797–804.
- 11 Chua SY, Ikram MK, Tan CS, et al. Relative contribution of risk factors for early-onset myopia in young asian children. *Invest Ophthalmol Vis Sci* 2015;56:8101–7.
- 12 Ombelet W, Martens G, De Sutter P, et al. Perinatal outcome of 12,021 singleton and 3108 twin births after non-IVF-assisted reproduction: a cohort study. *Hum Reprod* 2006;21:1025–32.
- 13 Hart R, Norman RJ. The longer-term health outcomes for children born as a result of IVF treatment. Part II—Mental health and development outcomes. *Hum Reprod Update* 2013;19:244–50.
- 14 Lazaraviciute G, Kauser M, Bhattacharya S, et al. A systematic review and meta-analysis of DNA methylation levels and imprinting disorders in children conceived by IVF/ICSI compared with children conceived spontaneously. *Hum Reprod Update* 2014;20:840–52.
- 15 Crawford C, Dearden L, Meghir C. When you are born matters: the impact of date of birth on child cognitive outcomes in England, see discussion paper no. 93 2007.
- 16 Ponzio M, Scoppa V. The long-lasting effects of school entry age: evidence from Italian students. *J Policy Model* 2014;36:578–99.
- 17 Hyman L, Gwiazda J, Hussein M, et al. Relationship of age, sex, and ethnicity with myopia progression and axial elongation in the correction of myopia evaluation trial. *Arch Ophthalmol* 2005;123:977–87.
- 18 Mutti DO, Mitchell GL, Moeschberger ML, et al. Parental myopia, near work, school achievement, and children's refractive error. *Invest Ophthalmol Vis Sci* 2002;43:3633–40.
- 19 Jones-Jordan LA, Mitchell GL, Cotter SA, et al. Visual activity before and after the onset of juvenile myopia. *Invest Ophthalmol Vis Sci* 2011;52:1841–50.
- 20 Rose KA, Morgan IG, Ip J, et al. Outdoor activity reduces the prevalence of myopia in children. *Ophthalmology* 2008;115:1279–85.
- 21 Williams C, Miller LL, Gazzard G, et al. A comparison of measures of reading and intelligence as risk factors for the development of myopia in a UK cohort of children. *Br J Ophthalmol* 2008;92:1117–21.
- 22 van de Berg R, Dirani M, Chen CY, et al. Myopia and personality: the genes in myopia (GEM) personality study. *Invest Ophthalmol Vis Sci* 2008;49:882–6.
- 23 Saw SM, Tan SB, Fung D, et al. IQ and the association with myopia in children. *Invest Ophthalmol Vis Sci* 2004;45:2943–8.
- 24 Pärssinen O, Kauppinen M, Viljanen A. The progression of myopia from its onset at age 8–12 to adulthood and the influence of heredity and external factors on myopic progression. A 23-year follow-up study. *Acta Ophthalmol* 2014;92:730–9.
- 25 Zhang M, Gazzard G, Fu Z, et al. Validating the accuracy of a model to predict the onset of myopia in children. *Invest Ophthalmol Vis Sci* 2011;52:5836–41.
- 26 French AN, Morgan IG, Mitchell P, et al. Risk factors for incident myopia in Australian schoolchildren: the Sydney adolescent vascular and eye study. *Ophthalmology* 2013;120:2100–8.
- 27 Hashemi H, Khabazkhoob M, Asharlous A, et al. Cycloplegic autorefraction versus subjective refraction: the Tehran Eye Study. *Br J Ophthalmol* 2016;100:1122–7.