ORIGINAL ARTICLE

Birth Order and Myopia

Jeremy A. Guggenheim, George McMahon, Kate Northstone, Yossi Mandel, Igor Kaiserman, Richard A. Stone, Xiaoyu Lin, Seang Mei Saw, Hannah Forward, David A. Mackey, Seyhan Yazar, Terri L. Young, and Cathy Williams

1School of Optometry & Vision Sciences, Cardiff University, Cardiff, UK, 2School of Social and Community Medicine, University of Bristol, Bristol, UK, 3IDF Medical Corps HQ, Israel, and The Mina & Everard Goodman Faculty of Life Sciences, Bar Ilan University, Israel, 4Barzilai Medical Center, Ashkelon, Israel, 5Department of Ophthalmology, Scheie Eye Institute, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA, 6Saw Swee Hock School of Public Health, National University of Singapore, Singapore, 7Singapore Eye Research Institute, Singapore, 8Department of Genetics and Epidemiology, Centre for Ophthalmology and Visual Science, University of Western Australia, Lions Eye Institute, Perth, Australia, 9Center for Human Genetics, Duke University Medical Center, Durham, NC, USA, 10Department of Ophthalmology, Duke University Eye Center, Durham, NC, USA, and 11Centre for Child and Adolescent Health, University of Bristol, Bristol, UK

ABSTRACT

Purpose: An association between birth order and reduced unaided vision (a surrogate for myopia) has been observed previously. We examined the association between birth order and myopia directly in four subject groups.

Methods: Subject groups were participants in (1) the Avon Longitudinal Study of Parents and Children (ALSPAC; UK; age 15 years; N = 4401), (2) the Singapore Cohort Study of Risk Factors for Myopia (SCORM; Singapore; age 13 years; N = 1959), (3) the Raine Eye Health Study (REHS; Australia; age 20 years; N = 1344), and (4) Israeli Defense Force Pre-recruitment Candidates (IDFC; Israel; age 16–22 years; N = 888,277). The main outcome was odds ratios (OR) for myopia in first-born versus non-first-born individuals after adjusting for potential risk factors.

Results: The prevalence of myopia was numerically higher in first-born versus non-first-born individuals in all study groups, but the strength of evidence varied widely. Adjusted ORs (95% confidence intervals, CIs) were: ALSPAC, 1.31 (1.05–1.64); SCORM, 1.25 (0.89–1.77); REHS, 1.18 (0.90–1.55); and IDFC, 1.04 (1.03–1.06). In the large IDFC sample, the effect size was greater (a) for the first-born versus fourth- or higher-born comparison than for the first-born versus second/third-born comparison (p < 0.001) and (b) with increasing myopia severity (p < 0.001).

Conclusions: Across all studies, the increased risk of myopia in first-born individuals was low (OR < 1.3). Indeed, only the studies with >4000 participants provided strong statistical support for the association. The available evidence suggested the relationship was independent of established risk factors such as time outdoors/reading, and thus may arise through a different causal mechanism.

Keywords: Avon Longitudinal Study of Parents and Children, birth order, myopia, Raine Eye Health Study, refractive error, Singapore Cohort Study of Risk Factors for Myopia

INTRODUCTION

Myopia occurs when the length of the unaccommodated eye is too long relative to its optical power. This leads to symptoms of blurred distance vision, requiring the use of spectacles, contact lenses or refractive surgery. Furthermore, the axial elongation typically seen in myopia puts the eye at an increased risk of sight-threatening conditions such as retinal detachment, glaucoma, cataract, and chorioretinal
Both genetic and environmental factors are implicated in causing the high and increasing prevalence of myopia observed in many populations. Because myopia often develops during school-age, environmental risk factors present during this period have been studied intensively. A causal link between myopia and the amount of time children spend doing nearwork has been hypothesized for decades, with some support. However, careful longitudinal studies have suggested the influence of nearwork is limited. More recently, the time children spend outdoors has been shown to be negatively associated with myopia. Also, the discovery of associations between antenatal and early postnatal factors such as maternal age, parental smoking, birth weight, breastfeeding, and birth order has renewed interest in this period of early life and its role in refractive development.

A number of studies have assessed the relationship between birth order and myopia. However, all of these prior studies suffered from one of the following limitations: employing an indirect method of detecting myopia (namely, unaided distance vision of 6/12 or worse), categorizing those with myopia and hyperopia together, or investigating a highly selected group of subjects (closely inbred pedigrees). Here we report an investigation of the relationship between birth order and myopia in four groups that are largely representative of the general population in four different countries.

**MATERIALS AND METHODS**

**Subjects**

**Avon Longitudinal Study of Parents and Children (ALSPAC)**

ALSPAC recruited 14,541 pregnant women resident in Avon, UK, with expected dates of delivery between 1 April 1991 and 31 December 1992. Of the initial 14,541 pregnancies, 13,988 children were alive at 1 year. The original cohort was largely representative of the UK 1991 Census; however, families of low socioeconomic status, families in which the mother was a teenager at the birth of her child, and families of non-white ethnic origin were underrepresented. For the present study, subjects from multiple births (e.g. twins) or of non-Caucasian ethnicity (~2% of the total) were omitted from the analysis. During pregnancy, mothers were asked for details of all previous pregnancies resulting in either a live birth or stillbirth, from which the ALSPAC child’s birth order was derived.

**Singapore Cohort Study Of Risk Factors for Myopia (SCORM)**

Children aged 7–9 years at baseline attending three schools in Singapore were invited to participate. Individuals with syndromic myopia, congenital cataract, serious systemic diseases or who refused instillation of eyedrops were excluded. Of the 2819 eligible children, 1979 (70.2%) participated at baseline. Follow-up data were collected at yearly visits using the same clinical procedures as at baseline. For each SCORM participant, information on the number of siblings, and their ages, was obtained from the baseline questionnaire. Birth order was calculated from the sibling information.

**Raine Eye Health Study (REHS)**

The Western Australian Pregnancy Cohort (Raine) Study recruited 2868 individuals from Perth, Australia between 1989 and 1991. The original cohort was a population-based sample of Western Australians. Mothers were recruited into the study during the 18th week of pregnancy. Prenatal and birth data including birth order information were collected prospectively from participants’ mothers. Subjects from multiple births were omitted from the analysis.

**Israeli Defense Force Pre-recruitment Candidates (IDFC)**

Military service is compulsory in Israel except for specific minority groups. The IDFC sample comprised 888,277 subjects aged 16–22 years examined in pre-recruitment offices and who had refractive evaluation. All data were obtained from the database of the Israel Defense Forces Induction Center, without any details of personal identity. “Region of family origin” was categorized as Israeli, Western (European, American, or Oceanic), or Eastern (Asian or African) according to the father’s country of birth or, for any subject whose father was born in Israel, by the grandfather’s country of birth. The analysis was restricted to non-orthodox recruits, since refractive development has been reported to differ markedly in this group. Birth order was reported by the conscript as part of the pre-recruitment evaluation.

**Ethical approval**

Each study adhered to the tenets of the Declaration of Helsinki for research involving human subjects and received ethical approval from its local ethics committee: ALSPAC, the ALSPAC Law and Ethics Committee and the local research ethics committees; SCORM, the Singapore Eye Research Institute Ethics Committee; REHS, University of Western Australia Human Research Ethics Committee; IDFC, The Israel Defense Force Institutional Review Board.

**Refractive Errors and Potential Risk Factors**

**ALSPAC**

Noncycloplegic autorefraction measurements (Canon R50 instrument, Canon USA Inc, Lake Success, NY)
were obtained during a visit to a research clinic when the children were approximately 15 years old, as described. Spherical equivalent (SEq) for each eye was calculated as sphere power plus half cylinder power, and then averaged for the two eyes of each subject (SEqAV). Subjects were classified as “likely myopes” if they had an SEqAV ≤ −1.00 diopters (D) and as “likely non-myopes” otherwise. A validation study suggested the −1.00 D cut-point provided 96% specificity and 89% sensitivity (area under receiver operating characteristic curve 92%) in diagnosing myopia corresponding to a subjective refraction of ≤−0.50D. Subjects were classified, additionally, as “likely emmetropes/hyperopes” if they had an SEqAV ≥ −0.25 D, using the threshold previously adopted by Jones-Jordan. Socioeconomic status, intrauterine growth retardation (small for gestational age), maternal tobacco smoking during the first 3 months of pregnancy, maternal age, time spent outdoors, time spent reading for pleasure, and parental myopia were assessed as described previously. For first-born subjects, “only child” status was inferred if the mother reported that the study child had no siblings (related or foster children) living at home, in a questionnaire completed when the study child was aged 11 years.

SCORM
Details of the assessment of refractive error have been reported previously. Briefly, refractive error was measured by cycloplegic autorefraction using a Canon RK-5 autorefractor (Canon Ltd, Tochigiken, Japan), and subjects were classified as myopic if SEq refractive error in the right eye was ≤−0.50 D.

REHS
At age 20 years, 1344 participants underwent a comprehensive eye examination that included cycloplegic autorefraction (Nidek ARK-510A (Nidek Co. Ltd, Gamagori, Japan)). Complete ocular and general phenotypic data were available for 1266 (94.2%) participants. Subjects were diagnosed as myopic if SEq in their right eye was ≤−0.50D. At the examination, participants completed a questionnaire containing the question, “In summer, when not at work, how much time do you spend in the sun?” The questionnaire also asked how many parents were myopic. Other phenotypic information was available from the previous cohort follow-ups.

IDFC
Details of the assessment of refractive error have been reported previously. Briefly, subjects with unaided vision of 6/6 on a Snellen chart with not more than one mistake were assumed to be non-myopic. For subjects with corrected visual acuity of 6/6 (with not more than one mistake) the prescription of their optical correction was taken as their refractive error or the subject underwent a subjective refraction examination by an optometrist. All other subjects underwent subjective non-cycloplegic refraction. Subjects were classified as myopic if SEq refractive error in the right eye was ≤−0.50 D.

Statistical Analyses
Fisher’s exact test or the χ² test were used to compare subjects classified as myopic versus non-myopic by first-born status. Multivariate binary logistic regression was used to study the influence of multiple risk factors. To be included in the multiple regression model, a variable had to be associated with myopia status (p < 0.05) in univariate analysis and be associated with first-born status (p < 0.05) in univariate analysis. Note that we restricted attention to variables associated with both myopia status and first-born status in univariate analyses, since a variable not meeting our criterion for association with being first born was deemed unlikely to act as a confounder. The availability of information on potential risk factors for myopia in each study group is listed in the Results section, along with details of which variables were tested in univariate analyses, and those variables that were included in the final logistic regression model. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) are presented. Analyses were carried out using SPSS version 18 (SPSS Inc, Chicago, Illinois, USA).

For the IDFC and SCORM studies, where recruitment occurred over several years, some of the subjects included in the analysis were siblings. We developed a simulation model to assess whether the presence of siblings biased estimates of the risk of myopia associated with birth order (Appendix 1, online supplementary material). The simulation suggested that there would be minimal or no observable bias when analyses were conducted ignoring the relatedness between subjects. Theoretical reasoning suggested that, because of the study designs employed, the age of the subject was not a potentially confounding factor (Appendix 2, online supplementary material). This was important given that, within families, first-born children are always older than their second-born siblings, and so on, and since myopia tends to increase with age.

RESULTS
Demographics of the four samples studied are shown in Tables 1 and 2. Consistent with theoretical expectations (Appendix 2, online supplementary material), the age of subjects was found to be similar across birth orders (Table 2). The numbers of subjects classified as myopic in each cohort are shown in Table 3.
Several variables showed evidence of association with both likely myopia and with first-born status in univariate trials. Specifically, positive associations were observed for an increased number of myopic parents, a higher social class of parents, more time spent reading for pleasure and older maternal age. Adjusting for these covariates increased the estimated effect size for the association between first-born status and likely myopia (Table 5; adjusted OR 1.31, 95% CI 1.05–1.64). When the analysis described above was repeated using the comparison “likely myopia” versus “likely emmetropic/hyperopia” (as opposed to “likely myopia” versus “likely not myopia”) the effect size and statistical significance level were qualitatively the same (Table 5).

After excluding “only children” (children with no related/fostered brothers or sisters), the increased risk of likely myopia in first-born subjects remained
TABLE 4. Potential confounding variables for the four study groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ALSPAC Available</th>
<th>Univariate analysis</th>
<th>Included</th>
<th>SCORM Available</th>
<th>Univariate analysis</th>
<th>Included</th>
<th>REHS Available</th>
<th>Univariate analysis</th>
<th>Included</th>
<th>IDFC Available</th>
<th>Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>NA</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Parental myopia</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Time reading for pleasure</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Maternal age</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Smoking during pregnancy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Prematurity</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>✓</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Intelligence quotient</td>
<td>✓</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Body mass index</td>
<td>✓</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Height</td>
<td>✓</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Season of birth</td>
<td>✓</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Place of birth</td>
<td>NA</td>
<td>NA</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>NA</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

Available: tick indicates information on variable was available; Univariate analysis: tick indicates variable was tested in univariate analysis for association with birth order and myopia; Included: tick indicates risk factor was associated with both myopia and birth order, and was included in the final logistic regression model. aAll available potential confounders were included in the final model.

ALSPAC, Avon Longitudinal Study of Parents and Children; SCORM, Singapore Cohort Study of Risk Factors for Myopia; REHS, Raine Eye Health Study; IDFC, Israeli Defense Force Pre-recruitment Candidates; NA, Not applicable.
essentially unchanged (Table 5). This finding implied that the risk associated with being first born did not arise because of a peculiarly high prevalence of myopia in “only children”, but rather that all first-born children were at an increased risk of myopia regardless of whether or not they had younger siblings (specifically, the prevalence of “likely myopia” was 17.9% in “only children”, 18.0% in first-born children who had younger siblings, and 16.0% in children who were not first born).

Note that data for at least one risk factor variable were missing for 1882 out of the 4401 ALSPAC participants. Subjects with full information were an average of 14 days younger ($p < 0.001$) and −0.08 D more myopic ($p = 0.042$) than those with missing information. The proportion of boys and girls was the same in those with and without missing information, however subjects with full information were much more likely to be first-born subjects (54% vs 43%, $p < 0.001$).

**SCORM**

Prior to adjustment for other potential risk factors, being first born was associated with an increased risk of myopia in children in the SCORM study (OR 1.46, 95% CI 1.03–2.06). However, after adjusting for ethnicity, which was the only risk factor that was associated both with myopia and first-born status in univariate analyses, the magnitude and statistical evidence for the association between being first born and myopia was markedly reduced towards the null (OR 1.25, 95% CI 0.89–1.77, $p = 0.20$).

**REHS**

In unadjusted analyses, the prevalence of myopia was higher in first-born than in non-first-born subjects, but the degree of association was not significant (OR 1.04, 95% CI 0.80–1.34, $p = 0.79$). After adjusting for maternal age, which was the only variable associated both with myopia and first-born status in this cohort, the risk associated with being first born was shifted away from the null, but remained non-significant (OR 1.18, 95% CI 0.90–1.55, $p = 0.24$).

**IDFC**

After adjusting for region of family origin, socioeconomic status, intelligence, body mass index, height, birth place, season of birth, and sex, birth order was associated with all degrees of myopia in the IDFC sample (all $p < 0.001$; Table 6). Furthermore, for mild and moderate levels of myopia, the risk (OR) associated with being first born was greater in comparison to individuals with a birth order of four or more than in comparison to those who were second or third born in this study group. For high myopia, however, the risk in comparison to those who were


<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n OR (95% CI) p Value</td>
<td>n OR (95% CI) p Value</td>
</tr>
<tr>
<td>Including only children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likely myopic vs likely not myopic</td>
<td>4401 1.18 (1.01–1.38) 0.038</td>
<td>2499 1.31 (1.05–1.64) 0.016</td>
</tr>
<tr>
<td>Likely myopic vs likely emmetropic/hyperopic</td>
<td>2939 1.23 (1.05–1.46) 0.014</td>
<td>1679 1.41 (1.11–1.78) 0.004</td>
</tr>
<tr>
<td>Excluding only children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likely myopic vs likely not myopic</td>
<td>3527 1.16 (0.97–1.38) 0.102</td>
<td>2194 1.37 (1.07–1.74) 0.012</td>
</tr>
</tbody>
</table>

Note that sample size differs between the adjusted and unadjusted analyses due to missing information for some children. Adjusted analyses included the variables number of myopic parents, social class of parents, time spent reading for pleasure, and maternal age. OR, odds ratio; CI, confidence interval


<table>
<thead>
<tr>
<th>Degree of myopia</th>
<th>OR (95% CI)</th>
<th>p Value</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild ($&gt;-3.00$ and $\leq -0.50$D)</td>
<td>1.04 (1.03–1.06)</td>
<td>&lt;0.001</td>
<td>1.12 (1.09–1.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate ($&gt;-6.00$ and $\leq -3.00$D)</td>
<td>1.12 (1.09–1.14)</td>
<td>&lt;0.001</td>
<td>1.14 (1.10–1.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe ($\leq -6.00$D)</td>
<td>1.18 (1.13–1.23)</td>
<td>&lt;0.001</td>
<td>1.19 (1.11–1.27)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Analyses were adjusting for “region of family origin”, socioeconomic status, intelligence, body mass index, height, birth place, season of birth, and sex. OR, odds ratio; CI, confidence interval; D, diopters
second or third born (OR 1.18, 95% CI 1.13–1.23, \( p < 0.001 \)) was similar to that seen in comparison to those with a birth order of four or more (OR 1.19, 95% CI 1.11–1.27, \( p < 0.001 \)).

**DISCUSSION**

Overall, our findings from the four subject groups suggest that there is a small, increased risk of myopia in first-born vs non-first-born subjects, as implied previously from studies employing indirect refraction assessment methods.\(^{14,18,19}\) The association we observed in the largest study group (IDFC) is unlikely to have arisen by chance, while those seen in the other studies provided weaker evidence consistent with their smaller sample sizes, and thus need to be interpreted with caution. Nevertheless, all of the study groups showed a similar direction and (low) level of risk (Figure 1). In the largest study group, the IDFC, there was strong evidence of a greater difference in myopia prevalence in first-born versus fourth- or higher-born individuals compared to first-born versus second- or third-born individuals, as has already been reported for a large UK-based cohort, the National Survey of Health and Development.\(^{14}\) However, this relationship was not seen in the other groups we studied.

The lack of uniformity of the adjusted ORs across the four study groups (Figure 1) is likely to have been influenced by sample size-related variation in statistical power, as mentioned above. However, in addition, subject-related differences in the population groups that were investigated may also have had an impact; for instance, participants in the REHS and IDFC were generally older than those in SCORM and ALSPAC, the age range of the IDFC was wider than those of the other three cohorts, and a larger proportion of the SCORM participants were first born than was the case in the other cohorts. Furthermore, the level of exposure to environmental risk factors for myopia is thought to vary between Singapore, Israel, Australia and the UK.\(^{33}\) Differences in statistical analysis of the groups may also have contributed to the variability in the adjusted ORs; the availability and inclusion of potential confounding variables such as socioeconomic status and parental myopia differed markedly across the study groups (Table 4). These between-site differences can be viewed as an important limitation of our attempt to draw together results from different cohorts. Conversely, epidemiology studies that deliberately explore findings from disparate study populations also offer the attraction of providing some insurance against confounding,\(^{34}\) since a causal association, for instance, should produce a consistent magnitude and direction of effect across diverse study sites.

The low risk associated with being first born implies that birth order has less influence on refractive development compared to known risk factors for myopia such as parental refractive error and time spent engaged in sports/outdoor activity.\(^{2,25,26}\) In the ALSPAC study, adjustment for behaviors implicated in causing variations in myopia risk within a family actually increased the estimated effect size (unadjusted OR 1.18, adjusted OR 1.31). Thus, the data do not support the idea that the association between birth order and myopia is confounded by the behavioral differences we adjusted for, although other behavioral differences may be involved. There were small differences in the age and refractive error of ALSPAC subjects with and without missing data, along with a surprisingly large difference in the proportion of first-born individuals (43% vs. 54%, respectively), i.e. subjects in the adjusted analysis were not a random sample of all those attending the research clinic at this age, and in particular, parents of first-born children were more likely to have fully completed questionnaires about their child (moreover, attendance of ALSPAC children at the research clinic is also known to vary depending on the age, sex and socioeconomic status of the participant\(^{28}\)). Potentially, the risk factor-myopia relationship profile of subjects with full vs missing information could also have varied. These demographic and potential risk profile differences may have contributed to the observed difference between the unadjusted and adjusted OR estimates, meaning that caution is needed in extrapolating these values to the entire population.

Our novel finding that “only children” appeared to be at a similarly elevated risk of myopia as first-born children with younger siblings adds weight to the hypothesis that birth order confers an increased risk of myopia independent of known risk factors, since it argues against a causal mechanism involving...
first-born children modifying the myopia-related environmental risk factor exposure of their younger siblings.

Birth order could conceivably be linked causally to myopia via a direct physiological mechanism, for example relating to the in utero environment. An association between birth order and refraction could also arise if maternal age (or paternal age) is a risk factor for myopia in offspring. Supporting potential confounding between birth order and maternal age, Rudnicka\textsuperscript{14} reported an elevated risk of reduced uncorrected vision (i.e. likely myopia) with increasing maternal age (OR 1.10 per 5-year increase, 95% CI 1.04–1.17) in a meta-analysis of three UK-based cohorts. In a more detailed analysis of one of the Rudnicka study samples, Rahi\textsuperscript{13} found evidence pointing towards a complex relationship in which both low and high maternal age increased the risk of myopia compared with a maternal age between 21 and 30 years, along with a further rise in risk in those born to mothers aged ≥35 years (OR 1.5, 95% CI 1.1–2.0). However, in regression models that adjusted for maternal age, birth order appeared to confer an independent risk for myopia in the three groups of subjects studied by Rudnicka\textsuperscript{14}, and this was also the case for the ALSPAC participants studied here.

Although there are reports of birth order-disease associations with a physiological basis unconnected to maternal age, for instance in conditions such as metabolic syndrome, schizophrenia, asthma and cancer,\textsuperscript{35–38} the causal pathways involved are not generally known. First-born babies tend to have a lower birth weight for their gestational age than non-first-born babies (sometimes termed “small for dates”)\textsuperscript{39} and are over-represented in those non-first-born babies (sometimes termed “small for dates’’)\textsuperscript{39} and are over-represented in those non-first-born babies (sometimes termed “small for dates’’).\textsuperscript{39} Given the evidence from animal models for a role of glucagon and insulin in emmetropization,\textsuperscript{43,44} this raises the interesting possibility that altered signaling through the insulin/glucagon axis relating to birth order may impact not only on bodily growth but also on ocular growth.

A higher prevalence of myopia has been observed repeatedly in communities living in urban rather than rural locations.\textsuperscript{45–47} An interesting implication of an association between birth order and myopia is that it has the potential to contribute to this difference in prevalence, because the birth rate (or, strictly, the total fertility rate) of women living in urban regions is typically lower than that of women living in rural areas, after accounting for any difference in child mortality rates (see US Agency for International Development-funded Monitoring and Evaluation to Assess and Use Results Demographic and Health Surveys project, http://www.measuredhs.com/). We constructed a simulation model (details available on request) to test the likely magnitude of birth order in contributing to the urban vs rural myopia prevalence rates (assuming the following causal path: Low birth rate → high proportion of subjects who are first born → increased prevalence of myopia → other causes). The results suggested that the birth order-myopia association would account for differences in prevalence of <5%, i.e. much less than the often marked difference in myopia prevalence between urban and rural locations.\textsuperscript{15–47}

To summarize, the strength of our presentation of these studies is that it facilitates the comparison of multiple groups of subjects of differing age, ethnicity and myopia prevalence, enabling us to examine the generality of the myopia-birth order association, and the very large sample size of the IDFC cohort. Weaknesses affecting cross-study comparison are that non-uniform assessment methods were employed across study groups, that cycloplegia was not used to assess refractive error in all study groups, that the range of potential myopia risk factors used in the regression analyses was not uniform across study groups, and that none of the groups of subjects was fully representative of the general population. Indeed, for the above reasons we decided that it would be inappropriate to perform a meta-analysis of the results in the four subjects groups. Furthermore, we made no attempt to search for interactions between birth order and other potential myopia risk factors, due to a perceived lack of statistical power in the three smaller study groups and lack of information about key risk factors in the IDFC. Such analyses may be an interesting avenue for further research.

In conclusion, we found robust evidence in the two largest studies that being a first-born child increased the risk of myopia to a small extent, substantiating the conclusions of existing studies that relied on more indirect methods. Being first born was also a risk factor for high-degree myopia. Moreover, adjusting for known myopia risk factors and excluding “only children” did little to modify the risk associated with being first born, suggesting the possibility of an independent mechanism of action (perhaps of physiological and maternal origin). In the Israeli subjects, there was also support for a relationship of decreasing risk of myopia with increasing birth order. There is uncertainty regarding whether these associations hold true for the smaller studies and/or whether they might vary in different ethnicities, but the data are suggestive that the association between birth order and myopia is a widespread phenomenon. Future epidemiological studies could help confirm or refute this by routinely collecting and reporting information on participants’ birth orders. If there are other (non-behavioral) causal mechanisms involved it may be
ininformative to explore their contribution to myopia development.

ACKNOWLEDGEMENTS

The ALSPAC researchers are extremely grateful to all the families who took part in this study, the midwives for their help with recruitment, and the other members of the ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The Raine researchers thank all participants and their families and the whole Raine Study team.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. Funding and support was provided by the UK Medical Research Council [Grant ref: 74882] the Wellcome Trust [Grant ref: 076467] and the University of Bristol provide core support for ALSPAC. The Raine Eye Health Study was funded by the Australian Foundation for the Prevention of Blindness, The Ophthalmic Research Institute of Australia (ORIA) and the National Health and Medical Research Council (NHMRC Grant ref: 1021105). The Western Australian Pregnancy Cohort (Raine) Study core funding is provided by The University of Western Australia (UWA), The Telethon Institute for Child Health Research, Raine Medical Research Foundation, UWA Faculty of Medicine, Dentistry and Health Science, Women’s and Infant’s Research Foundation, Curtin University, NHMRC. This work was specifically funded [Grant: SClAD 053] by the National Eye Research Centre, Bristol (JAG, CW), a National Institute for Health Research career development fellowship (CW), National Institutes of Health [Grant: R01-EY018838] (RAS), the Paul and Evanina Bell Mackall Foundation Trust (RAS), Research to Prevent Blindness (RAS), and Singapore National Medical Research Council [Grant: NMRC/0695/2003] (SMS).

REFERENCES


