Myopia Over the Lifecourse: Prevalence and Early Life Influences in the 1958 British Birth Cohort

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Purpose: To investigate the hypothesis that the excessive growth of the eye in myopia is associated with general growth and thus influenced by early life biological and social factors, and that these associations underlie recent secular trends of increasing prevalence and severity of myopia.

Design: Cohort study.

Participants: A total of 2487 randomly selected 44-year-old members of the 1958 British birth cohort (27% subsample).

Methods: Diverse and detailed biological, social, and lifestyle data have been collected by following members since birth through a series of clinical examinations or face-to-face interviews carried out by trained examiners. At 44 years, cohort members underwent autorefraction using the Nikon Retinomax 2 (Nikon Corp., Tokyo, Japan) under non-cycloplegic conditions. A lifecourse epidemiologic approach, based on 4 sequential multivariable “life stage” models (preconceptional; prenatal, perinatal, and postnatal; childhood; and adult), was used to examine the influence of early life biological, social and lifestyle factors, growth patterns, and “eye-specific” factors on myopia.

Main Outcome Measures: Myopia severity (all, mild/moderate: spherical equivalent −0.75 to −5.99 diopters [D]; severe: ≥ −6.00 D extreme vs. emmetropia −0.74 to +0.99 D) and myopia onset (early [< 16 years] vs. later).

Results: A total of 1214 individuals (49%; 95% confidence interval, 48.8 –50.8) were myopic (late onset in 979 [80.6%]). Myopia was positively associated with low birthweight for gestational age, gender, greater maternal age, higher paternal occupational social class, and maternal smoking in early pregnancy. Myopia was independently associated with proxy markers of near work and educational performance, with some differences by onset and severity. In adults, greater height and higher educational attainment and socioeconomic status were associated with myopia.

Conclusions: Trends in the key influences on child health and growth identified as novel putative risk factors in this study are consistent with global trends of increasing myopia: increasing births to older mothers, increasing rates of intrauterine growth retardation and survival of affected children, increasing persistence of smoking in pregnancy, and changing socioeconomic status. Prospects for prevention of myopia would be improved by a paradigm shift in myopia research, with lifecourse and genetic epidemiologic approaches applied in tandem in large unselected populations.

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Refractive error, predominantly myopia (shortsightedness), is the most common eye disease and thus the major cause of reduced vision internationally.1 High attendant societal costs include loss of productivity and comorbidity due to vision impairment per se, as well as the direct costs of correction through glasses, contact lenses, and surgical treatment.5 Myopia is a priority of VISION 2020, the global multi-agency initiative against visual impairment.8 Mild or moderate myopia currently affects at least 25% of populations in Europe and North America, approximately 5% in Africa, and up to 80% in East Asia.4–9 By contrast, “pathologic” myopia (very severe and sometimes “syn- dromic”) affects less than 3% of most populations.4–6,8,9 Some populations seem to have experienced striking increases in the prevalence of mild or moderate myopia in the past few decades, for example, by 25% in some East Asian settings,1,6 where these secular trends have also been accompanied by shifting population distributions toward increasing severity and younger age at onset.7,9–11 The drivers of these changes are likely to be “environmental,” namely, social and lifestyle factors mediated through biological determinants operating against the less fluid background of genetic predisposition.7,12,13 Since Kepler in the early 17th century, researchers have prioritized investigation of “eye-specific” factors, in particular the role of retinal blur (defocus) affecting the peripheral...
retina, which occurs during “near work” viewing, such as in an educational context.14–18 This interest has recently expanded into more general consideration of the impact of the visual experiences of populations undergoing rapid economic development and urbanization.12,13,15–17 Time spent on outdoors activities is currently postulated to offer “protective” viewing conditions, although the nature of this effect is unclear.13,18–21

By contrast, we hypothesized that the excessive growth of the eye that underlies myopia is influenced by key early life influences on human growth, and that this association underlies some of the recent trends observed in myopia. We undertook a lifecourse epidemiologic investigation of myopia in a contemporary and nationally representative population of British adults. We report the prevalence of myopia (spherical equivalent ≥−0.75 diopeters [D] extreme) and its associations across the lifecourse with early life biological, social, and lifestyle factors, with growth patterns and eye-specific environmental factors, and dissect these relationships according to the timing of onset and severity of myopia to identify possible etiologic pathways.

Materials and Methods

Study Population

The 1958 British birth cohort originally comprised everyone born in Britain in 1 week in 1958.22 Diverse and detailed biological, social, and lifestyle data have been collected by following members since birth, through a series of clinical examinations or face-to-face interviews carried out by trained examiners. Specifically, ophthalmic data have been collected at 7, 11, 16, and 44 years.22 This population therefore offers a unique context for lifecourse investigations of ophthalmic disease.23

The ophthalmic assessment at 44/45 years included distance and near acuity, stereovision, and vision-related quality of life as part of a broader biomedical examination of the entire cohort.22 A random subsample also underwent autorefraction (automated measurement of refractive status of the eye) using the Nikon Retinomax 2 (Nikon Corp., Tokyo, Japan), under non-cycloplegic conditions. Refraction of all subjects was precluded by high equipment costs. Autorefraction in mid adult life avoids the systematic misclassification of individuals who appear to be emmetropic in childhood but develop myopia later.

The present study is based on 2487 individuals who underwent autorefraction, comprising a 27% random subsample of 9377 individuals assessed at age 44/45 years22 (after excluding 7 individuals post-refractive laser surgery whose prior refractions were unknown and 9 individuals with interocular discordance in refraction that crossed the emmetropic range). The overall biomedical assessment cohort comprised 78.3% of 11 971 individuals invited to participate and was representative of the original birth cohort,24 although there was some underrepresentation of male subjects and those of lower socioeconomic status at birth. Ninety-eight percent of the 1958 birth cohort is white compared with 89% of the current population in the United Kingdom.

Conceptual Framework for Analysis

To investigate possible causal associations, we developed a conceptual framework and constructed 4 sequential multivariable “life stage” models: preconceptional; prenatal, perinatal, and postnatal; childhood; and adult life. Each model was also adjusted for factors found to be significantly associated with refractive error (at $P≤0.1$) at any earlier life stage. Thus, the size and strength of the association of any given factor are interpreted in relation to the life stage in which it first occurs, and its influence over the lifecourse is assessed by examining any change in effect estimates across successive models. This enables interrelated factors to be assessed and possible pathways of action to be highlighted.

Primary Outcomes

All individuals in the study were classified according to refractive status at 44 years to avoid the potential for misclassification of individuals with late-onset myopia. Spherical equivalent quantifies the refractive status of an eye in a single summary measure (algebraic sum in D, sphere + 0.5 cylinder). Individual eyes were categorized using clinically meaningful (“treatment”) thresholds across the spherical equivalent distribution: severe myopia (spherical equivalent ≥−6.00 D extreme), moderate or mild myopia (−0.75 to −5.99 D), emmetropia (no refractive error, −0.74 to +0.99 D), and hypermetropia (long-sightedness ≥+1.0 D extreme). All individuals with myopia, based on mean spherical equivalent, were also dichotomized as early (by 16 years, by convention) or late onset, using a combination of information from prior examinations, parental reports, including use of glasses, and medical notes at 7, 11, and 16 years, in the absence of serial refraction data. Thus, there were 3 myopia outcome variables: presence per se (i.e., all myopia), timing of onset (i.e., early [by 16 years] vs. later), and severity (i.e., mild/moderate vs. severe).

Explanatory Variables

We examined a priori key factors known to be linked to general growth and growth patterns per se, as well as previously reported eye-specific environmental factors. These are shown grouped by life stage in Table 1 (available at http://aaojournal.org).25–29

Statistical Methods

We used mean spherical equivalent of the 2 eyes for each individual for estimation of prevalence of myopia to allow comparison with published data.

For the lifecourse analyses of myopia, overall and by severity, we used the spherical equivalent for each eye. Bivariate logistic and multinomial regression using sandwich variance estimates was used to model the paired data (2 eyes) and allow for correlation within individuals. We undertook univariable analysis and then built multivariable models for each life stage, as described earlier. For analysis of time of myopia onset, a similar strategy was followed using multinomial regression, based on individuals. For all analyses emmetropia was the reference category.

All analyses were carried out using Stata 9.2 (StataCorp, College Station, TX). Ethics approval for the biomedical study was obtained from South East Multicentre Research Ethics Committee (MREC) (ref: 01/1/44). This study is part of a broader program of work approved by the Institute of Child Health’s Research Ethics Committee. Cohort members gave individual informed consent to participate in the study.

Results

Frequency of Refractive Error

A total of 1214 cohort members (49%, 95% confidence interval [CI], 48.8–50.8) were myopic (spherical equivalent ≥−0.75 D
extreme). Of these, 979 (80.6%) had late-onset myopia and 235 (19.4%) had early-onset myopia (<16 years). Only 61 individuals (2.4%, 95% CI, 1.8–3.1) had severe myopia (≥6 D), all non-syndromic. A total of 1053 individuals (42.3%, 95% CI, 40.4–44.3) were emmetropic (no refractive error) and 220 individuals (8.8%, 95% CI, 7.7–10.0) were hypermetropic (long-sighted, mean spherical equivalent of ≥+1.0 D extreme).

Assessment of Associations between Myopia and General Growth, Determinants, and “Eye-Specific” Environmental Factors

These lifecourse analyses were based on data from 1866 of 2267 cohort members (82%) who had myopia or were emmetropic and for whom data on key early-life explanatory factors were complete. Some data on breastfeeding and highest educational achievement of cohort member were missing, 11% and 13%, respectively, as indicated in Tables 5 and 9. Descriptive statistics on the study population are shown in Table 2 (available at http://aaojournal.org).

Findings are presented in the chronologic life stage sequence described previously. We examined a large number of factors known to influence growth, but for clarity and brevity, we present only those factors (Table 1, available at http://aaojournal.org) most clearly associated with myopia in multivariable analysis.

Preconceptional Life Stage

Myopia was significantly associated with greater maternal age, increasing maternal height, and higher paternal occupational social class (Table 3). There were strong associations between greater maternal age and both greater severity and younger onset of myopia.

Higher paternal occupational social class was associated with early-onset and more severe myopia. The association with social class was significantly attenuated in the later life stage models, suggesting that its influence was mediated through other relevant childhood factors, for example, education and growth (Table 4, available at http://aaojournal.org).

There was some evidence for an association of myopia with greater maternal height (1% increase in risk per centimeter increase in height) and being firstborn (risk ratio \[ RR \] = 1.21; CI, 0.99–1.48 and \[ RR \] = 1.72; CI, 0.89–3.35 for mild/moderate and high myopia, respectively).

Prenatal, Perinatal, and Early Postnatal Life Stage

Myopia (overall, by severity, and by timing of onset) was significantly associated with having a lower birthweight adjusted for gestational age and gender. Greater severity of myopia was independently associated with maternal smoking in early pregnancy (Table 5).

Myopia was associated with lower birth weight for gestational age and gender, with lower birthweight but not with low gestational age per se. Thus, birthweight adjusted for gestational age and gender was retained in the analyses as an indicator of an “adverse” fetal environment leading to intrauterine growth retardation. Although all myopia outcome measures were associated, the strongest association was with high myopia. These associations, in relation to mild/moderate and late-onset myopia, were strengthened by adjusting for earlier life stage factors and further increased when considered in the subsequent life stage model, suggesting amplification or cascading of prenatal effects through the lifecourse (Table 6, available at http://aaojournal.org).

Maternal smoking during pregnancy was not associated with myopia, but when timing of exposure was considered, smoking in the first trimester compared with throughout pregnancy was associated with high myopia. This was independent of birthweight for gestational age. There was some evidence that breastfeeding, for even a short period (≤1 month), was “protective” against myopia.

Childhood Life Stage

Myopia was significantly associated with proxy markers of greater educational near work and educational performance, with some differentiation by onset and severity. Markers of socioeconomic deprivation in early childhood were not associated with myopia (Table 7).

Less severe and late-onset myopia were associated with higher standardized reading score at age 7 years (23% and 25% increase in risk, respectively, per standard deviation increase in score). General ability test score at 11 years, a marker of intelligence, was associated with early-onset myopia and more strongly associated with severe than with mild/moderate myopia. These associations were not significantly altered by adjustment for earlier life stage factors (Table 8, available at http://aaojournal.org).

Eighty-nine percent of subjects reported playing sports outside school hours at age 11 years (boys more than girls). High myopia was associated with playing sports less frequently (“only sometimes,” \[ RR \] = 1.83, CI, 0.96–3.47; “hardly ever,” \[ RR \] = 2.14, CI, 0.96–4.71).
At 16 years, there was a similar association between high myopia and participation in sports or outdoor activities. These associations were reduced after adjustment for earlier life stage models.

More severe and earlier-onset myopia were associated with greater height and lower body mass index at pre- and postpubertal ages in childhood (Fig 1), irrespective of gender (although there was some evidence for gender-specific growth trajectories, data not shown). Notably these associations were unchanged by adjustment for earlier life stage factors, suggesting direct correlations during childhood.

**Adult Life Stage**

Myopia was associated with higher educational attainment/duration and higher (non-manual) occupational social class (Table 9). Mild/moderate myopia was associated with greater adult total height, and more severe myopia was associated with greater sitting height (more sensitive to pre-pubertal growth), rather than leg length (more sensitive to early life/preschool growth). There was no association with adult body mass index. These associations were all attenuated to some degree by adjustment for significant factors from the prenatal, peri-/neonatal, and childhood models described earlier, suggesting they at least partly reflected early life etiologic pathways and childhood growth patterns (Table 10, available at http://aaojournal.org).

**Discussion**

Our findings suggest that at least 1 in 3 working-age adults in the United Kingdom have clinically significant myopia. Most have an onset (or first manifestation) in very late adolescence or early adult life. Myopia risk, severity, and timing of onset are associated with key environmental influences on prenatal growth and health, sometimes in potentially opposing directions of effect. For example, higher socioeconomic status is associated with increased risk of myopia but is protective against intrauterine growth retardation. Myopia was associated with higher educational attainment/duration and higher (non-manual) occupational social class (Table 9). Mild/moderate myopia was associated with greater adult total height, and more severe myopia was associated with greater sitting height (more sensitive to pre-pubertal growth), rather than leg length (more sensitive to early life/preschool growth). There was no association with adult body mass index. These associations were all attenuated to some degree by adjustment for significant factors from the prenatal, peri-/neonatal, and childhood models described earlier, suggesting they at least partly reflected early life etiologic pathways and childhood growth patterns (Table 10, available at http://aaojournal.org).

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### Table 5. Prenatal and Early Postnatal Life Stage: Factors Significantly Associated with All Myopia, Myopia by Severity, and Time of Onset (Model Adjusted for Significant Preconceptional Factors)

<table>
<thead>
<tr>
<th>Factors</th>
<th>All Myopia</th>
<th>Mild/Moderate Myopia</th>
<th>High Myopia</th>
<th>Early Onset</th>
<th>Late Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 2085</td>
<td>N = 1982</td>
<td>N = 103</td>
<td>N = 184</td>
<td>N = 814</td>
</tr>
<tr>
<td>Birth weight for gestational age and gender (standardized)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1289 1</td>
<td>1229 1</td>
<td>60 1</td>
<td>116 1</td>
<td>503 1</td>
</tr>
<tr>
<td>Early pregnancy only</td>
<td>159 1.1 (0.8–1.6)</td>
<td>144 1.1 (0.8–1.5)</td>
<td>15 2.4 (1.1–5.4)*</td>
<td>18 1.4 (0.8–2.5)</td>
<td>57 1.0 (0.7–1.5)</td>
</tr>
<tr>
<td>Throughout pregnancy</td>
<td>637 0.9 (0.7–1.1)</td>
<td>609 0.9 (0.8–1.1)</td>
<td>28 0.8 (0.4–1.5)</td>
<td>50 0.8 (0.5–1.2)</td>
<td>254 0.9 (0.7–1.1)</td>
</tr>
<tr>
<td>Ever breastfed‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>534 1</td>
<td>502 1</td>
<td>32 1</td>
<td>48 1</td>
<td>206 1</td>
</tr>
<tr>
<td>Yes</td>
<td>1321 0.9 (0.7–1.1)</td>
<td>1264 0.9 (0.8–1.1)</td>
<td>57 0.6 (0.4–1.2)</td>
<td>118 0.9 (0.6–1.3)</td>
<td>513 0.9 (0.7–1.1)</td>
</tr>
</tbody>
</table>

CI = confidence interval.

*P < 0.05.

N = number of eyes for myopia by severity and number of individuals for early/late-onset myopia.

§ Missing data on breastfeeding for 207 cohort members; missing category used in analysis.

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### Table 7. Childhood Life Stage: Factors Significantly Associated with All Myopia, Myopia by Severity, and Time of Onset (Model Adjusted for Significant Preconceptional, Prenatal, and Early Postnatal Factors)

<table>
<thead>
<tr>
<th>Factors</th>
<th>All Myopia</th>
<th>Mild/Moderate Myopia</th>
<th>High Myopia</th>
<th>Early Onset</th>
<th>Late Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 2085</td>
<td>N = 1982</td>
<td>N = 103</td>
<td>N = 184</td>
<td>N = 814</td>
</tr>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>Risk Ratio (95% CI)</td>
<td>Risk Ratio (95% CI)</td>
<td>Risk Ratio (95% CI)</td>
<td>Risk Ratio (95% CI)</td>
</tr>
<tr>
<td>Reading test at 7 yrs (z score)</td>
<td>1.2 (1.1–1.4)†</td>
<td>1.2 (1.1–1.4)†</td>
<td>1.0 (0.6–1.5)</td>
<td>1.1 (0.9–1.5)</td>
<td>1.3 (1.1–1.5)†</td>
</tr>
<tr>
<td>General ability test at 11 yrs (z score)</td>
<td>1.1 (1.0–1.3)†</td>
<td>1.1 (1.0–1.3)†</td>
<td>1.8 (1.2–2.6)†</td>
<td>1.7 (1.3–2.2)†</td>
<td>1.1 (0.98–1.3)*</td>
</tr>
<tr>
<td>BMI at 11 yrs</td>
<td>1.0 (0.9–1.1)</td>
<td>1.0 (0.9–1.1)</td>
<td>0.6 (0.4–0.8)†</td>
<td>0.9 (0.7–1.1)</td>
<td>1.0 (0.9–1.1)</td>
</tr>
<tr>
<td>Height in meters at 11 yrs</td>
<td>1.0 (0.9–1.1)</td>
<td>1.0 (0.9–1.2)</td>
<td>1.3 (1.0–1.7)†</td>
<td>1.1 (0.9–1.3)</td>
<td>1.0 (0.9–1.2)</td>
</tr>
</tbody>
</table>

BMI = body mass index; CI = confidence interval.

*P < 0.1 and P ≥ 0.05.

†P < 0.05.

‡N = number of eyes for myopia by severity and number of individuals for early/late-onset myopia.
dation, an independent risk factor for myopia in our study. The patterns of these associations suggest a complex picture of causality across the lifecourse, which implies direct effects in the prenatal period, setting trajectories of ocular growth, with indirect effects during childhood, acting to modify ocular growth patterns (Fig 2, available at http://aaojournal.org). Risk, severity, and onset of myopia are also associated independently with greater height in childhood and eventual adult stature, as well as growth rate in childhood. Our findings also replicate previously reported associations between myopia and educational near work, attainment and performance in childhood and adult life, and reduced outdoor activity, but suggest that these are at least partly determined or influenced by early life factors. Our study demonstrates the value of considering severity or timing of onset of myopia in addition to risk overall to illuminate putative relationships. Finally, our findings highlight that such “pathways” of association may be obscured without a hierarchic and longitudinal analytic approach over the lifecourse.

Our study has unique strengths conferred by the detailed longitudinal study of a large, nationally representative and contemporary population of adults that enabled information on key biological and social determinants of health and disease to be collected before eliciting refractive status. The study was undertaken at an appropriate stage of natural history that avoids substantial and systematic misclassification of refractive status outcome. Nevertheless, its context within a broader study of health meant that refraction was available on only a random subsample of the cohort, which may have limited the power to detect with consistency small but informative associations, for example, associations with being first born and later menarche (data not shown) that did not reach statistical significance. Detailed data are not available on some risk factors relating to visual experience, for example, direct measures of cumulative near work.

The prevalence of myopia in our population-based study, 49% using a threshold of $-0.75 \text{D}$, is higher than might have been anticipated. However, this is in agreement with contemporary data, which use slightly more conservative thresholds, in ethnically similar populations and emphasizes the high population burden of this disorder. The use of non-cycloplegic refraction provides robust data in the

Figure 1. Growth: height and body mass index at 7, 11, and 16 years in those with high, mild/moderate, or early-onset myopia (adjusted for early life factors). BMI = body mass index.

Table 9. Adult Factors Significantly Associated with All Myopia, Myopia by Severity, and Time of Onset (Model Adjusted for Significant Preconceptional, Prenatal, Early Postnatal, and Childhood Factors)

<table>
<thead>
<tr>
<th>Factors</th>
<th>All Myopia</th>
<th>Mild/Moderate Myopia</th>
<th>High Myopia</th>
<th>Early Onset</th>
<th>Late Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds Ratio (95% CI)</td>
<td>Risk Ratio (95% CI)</td>
<td>Risk Ratio (95% CI)</td>
<td>Risk Ratio (95% CI)</td>
<td>Risk Ratio (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Highest educational achievement</td>
<td>2085</td>
<td>1982</td>
<td>103</td>
<td>184</td>
<td>814</td>
</tr>
<tr>
<td>O level</td>
<td>829</td>
<td>1</td>
<td>607</td>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td>A level</td>
<td>349</td>
<td>1.2 (0.9–1.6)*</td>
<td>328</td>
<td>1.2 (0.9–1.6)</td>
<td>21</td>
</tr>
<tr>
<td>Higher education</td>
<td>643</td>
<td>1.4 (1.1–1.7)*</td>
<td>607</td>
<td>1.4 (1.1–1.8)</td>
<td>36</td>
</tr>
<tr>
<td>Social class at 42 yrs</td>
<td>2085</td>
<td>1982</td>
<td>103</td>
<td>184</td>
<td>814</td>
</tr>
<tr>
<td>Manual</td>
<td>662</td>
<td>1</td>
<td>741</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Non-manual</td>
<td>1423</td>
<td>1.2 (1.0–1.5)*</td>
<td>1344</td>
<td>1.2 (1.0–1.5)</td>
<td>79</td>
</tr>
<tr>
<td>Adult height ($z$ score)</td>
<td>2085</td>
<td>1.2 (1.0–1.4)</td>
<td>1982</td>
<td>1.2 (1.0–1.4)</td>
<td>103</td>
</tr>
<tr>
<td>Sitting height ($z$ score)</td>
<td>2085</td>
<td>1.0 (0.9–1.2)</td>
<td>1982</td>
<td>1.0 (0.9–1.1)</td>
<td>103</td>
</tr>
<tr>
<td>Leg length ($z$ score)</td>
<td>2085</td>
<td>1.1 (0.95–1.3)</td>
<td>1982</td>
<td>1.1 (1.0–1.3)</td>
<td>103</td>
</tr>
</tbody>
</table>

*P<0.1 and P<0.05.
†P<0.05.
‡N = number of eyes for myopia overall and by severity and number of individuals for early/late-onset myopia.
§Missing data on highest educational achievement of cohort member for 241 cohort members; missing category used in analysis.
context of a population survey of middle-aged adults, although it is recognized to result in overestimates of prevalence of myopia in children. The high proportion of late-onset myopia in the predominantly ethnically white population in our and prior research contrasts starkly with the young age of onset reported recently in East Asian populations who have undergone relatively rapid urbanization and economic transition. Underlying differences in genetic susceptibility are clearly a critical factor and may be sufficiently important to prevent or modify the impact of powerful “environmental” drivers, rendering uniform changes of the same scale in population age distribution unlikely in all ethnic groups in the United Kingdom. When comparable population-based studies of refractive error are undertaken and reported in the United Kingdom in the future, investigation of cohort effects would be of interest, particularly in different ethnic groups.

In the recent literature, greatest attention has been paid to “eye-specific” risk factors as the putative main drivers of secular trends in myopia, in particular the roles of educational or other “near work” activities, time spent outdoors, and exposure to ambient lighting. By contrast, our findings, especially in relation to associations with intrauterine growth retardation and the role of smoking in early pregnancy (which agrees with the animal experimental and pharmacologic literature but contrasts with prior epidemiologic reports), indicate the fundamental importance of prenatal and early life influences, and are consistent with an abnormal ocular growth trajectory determined in utero and amplified or cascaded during childhood. This mirrors established thinking about the role of prenatal “programming” or “patterning” during critical periods of growth in other “classic” complex chronic disorders, such as hypertension, diabetes, and obesity, which are thought to arise from a combination of genetic and environmental factors and interactions between them across the lifecourse, reflecting developmental plasticity and often involving “catch up” growth through organogenesis.

Trends in the key influences on child health and growth identified as novel putative risk factors in our study are consistent with global trends of increasing myopia: increasing births to older mothers, increasing rates of intrauterine growth retardation (small for gestational age), persistence of smoking in pregnancy (particularly among younger mothers), changing socioeconomic status, and declining rates of breastfeeding. The shifting distributions of refractive error mirror changes in the average height and growth patterns of children and their eventual adult stature (all associated with myopia in our study), and it may be relevant that these have occurred in more compacted timescales in some populations in whom myopia is now highly prevalent. Growth in childhood is increasingly recognized to be a major influence on long-term health outcomes. Thus, we suggest that “upstream” influences on human growth in general that accompany “urbanization” may be as relevant to controlling ocular growth and myopia progression as the “downstream” influences of visual experience that have until now been the focus of myopia research. This highlights the interesting prospect of cohort effects in refractive error as emerging trends in maternal and child health evolve.

In conclusion, there is a need for a new paradigm for myopia research. We advocate the application of genetic and lifecourse epidemiologic and statistical approaches in tandem in large unselected populations, studied longitudinally and across the lifecourse, to understand the prenatal and early life biological, social, and lifestyle influences on refractive error and their relationships with genetic determinants and “eye-specific” factors relating to visual experience in later life. Such integrated investigations are important for identifying etiologic pathways and thus modifiable risk factors, without which prospects for prevention or modification of this globally important disorder are likely to remain limited.

**References**


Footnotes and Financial Disclosures

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