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REVIEW

A review of environmental risk factors for myopia during early life, childhood and adolescence

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Myopia is a significant public health problem worldwide, particularly in East Asian countries. The increasing prevalence of myopia poses a huge socio-economic burden and progressive high myopia can lead to sight-threatening ocular complications. Hence, the prevention of early-onset myopia progressing to pathological high myopia is important. Recent epidemiological studies suggest that increased outdoor time is an important modifiable environmental factor that protects young children from myopia. This protective effect may be due to high light intensity outdoors, the chromaticity of daylight or increased vitamin D levels. This review summarises the possible underlying biological mechanisms for the protective association between time outdoors and myopia, including the potential role of nicotinic acetylcholine receptors in refractive error development. Recent evidence for the role of other environmental risk factors such as near work, birth seasons, parental smoking and birth order are also summarised.

Key words: children's vision, myopia, risk factors

Myopia is a significant public health problem across the globe, especially in East Asian countries like Singapore and China. The overall prevalence of myopia in adults aged above 40 years is 38.9 per cent in Singapore,[1] whereas it is much lower in Western countries like the United States[2] (25.1 per cent), Barbados[3] (21.9 per cent) and Australia[4] (15 per cent). Likewise, the prevalence of myopia is much higher in East Asian children. In 12-year-old children, the prevalence of myopia is 62.0 per cent in Singapore[5,6] and 49.7 per cent in Guangzhou, China[7] compared with 20.0 per cent in the United States,[8] 11.9 per cent in Australia,[9] 9.7 per cent in urban India[10,11] and 16.5 per cent in Nepal.[12] As a result of this high prevalence, the mean annual cost of myopia in Singapore teenagers is estimated to be US$148 per child due to eye examinations and optical purchases.[13] The mean annual cost of myopia is about US $709 per adult in Singapore due to eye examinations, optical purchases and laser in situ keratomileusis (LASIK) surgery.[14] Among US adults, the economic cost of myopia is estimated to be $4.6 billion per year.[15]

High myopia may lead to potentially blinding complications, such as retinal tears, myopic macular degeneration and choroidal neovascularisation in both adults[16] and adolescents[17] that may require surgery, medications, lifelong medical care as well as imposed high social costs.[18]

Both genetic and environmental factors play a role in the aetiology of myopia. Near work is an important environmental factor associated with myopia but recent evidence suggests that time spent outdoors is another modifiable risk factor.[19–22]

This paper provides a review of the major environmental factors that are associated with myopia during early life, childhood and adolescence, in contrast to a number of recent reviews that have mainly focused on the role of genetics in myopia.[23–25] This review not only considers time spent outdoors and near work but also other early life factors, such as parental smoking, birth season and post-natal light levels, birth order and maternal age that are associated with myopia.

ASSOCIATION BETWEEN TIME SPENT OUTDOORS AND MYOPIA

Evidence from epidemiological studies

Previous cross-sectional and cohort studies have shown a significant association between myopia and outdoor activity among Australian,[26,27] Singapore Chinese,[28] Taiwanese[29] and Caucasian children.[30–32]

In the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error study of six- to 14-year-old children of diverse ethnicities, time outdoors/sports activity was one to two hours lower in children who developed myopia compared to stable emmetropes ($p < 0.01$).[31] Similarly, in a recent population-based cohort study of 3,241 British children aged seven to 15 years,[20] children who spent more time outdoors had a lower risk of developing myopia compared to those who spent less time outdoors (hazards ratio [HR] = 0.75, 95 per cent CI: 0.60, 0.96, $p = 0.023$). Although physical activity also had an independent association with incident myopia, time outdoors was a stronger predictor for incident myopia than physical activity[20] (Table 1).

There are some potential limitations of this study.[20] Refractive error was measured using non-cycloplegic refraction, which tends to overestimate myopia in children.[20] This may result in the inadvertent misclassification of children into refractive error groups (incident myopia stable emmetropia), introducing some bias. There was also a significant loss to follow-up in older age groups (up to 85 per cent) and missing data (up

Author	Study design (location)	Sample size	Age	Definition of outdoor activity	Main findings
French et al.[21]	Population-based cohort study (Australia)	2103	6-12 years	Hours per week on outdoors	Increased OR for incident myopia in children with low and moderate levels of outdoor activity compared to those with high levels of outdoor activity.
Guggenheim et al.[20]	Population-based cohort study (ALSPAC†) (United Kingdom)	3241	7-15 years	Hours per day on outdoors/physical activity	Time spent outdoors and physical activity was significantly associated with incident myopia
Jones-Jordan et al.[31]	Longitudinal cohort (CLEERE‡) (United States)	731	6-14 years	Hours per week on sports/outdoor activities	Reduced time spent outdoors in children who became myopic compared to emmetropes
Jones-Jordan et al.[32]	Population-based cohort study (CLEERE) (United States)	835	6-14 years	Hours per week on outdoor/ sports activity	No significant association between time spent outdoors and myopia progression

†Avon Longitudinal Study of Parents and Children
‡Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error study

Table 1. Association between outdoor activity and myopia – evidence from epidemiological studies

to 13 per cent). Consequently, the association between myopia and time spent outdoors may have differed between children who remained in the study compared to those who discontinued.

In another population-based cohort study[21] of six- and 12-year-old Australians, including Caucasian and East Asian children, those with low and moderate levels of outdoor activity were more likely to develop myopia compared to children who performed more outdoor activity in both the younger (adjusted odds ratios [ORs] = 2.84, 95 per cent CI: 1.56, 5.17 and 1.14, 95 per cent CI: 0.59, 2.21, respectively for low and moderate groups, $p_{trend} < 0.0001$) and older cohort (adjusted ORs = 2.15, 95 per cent CI: 1.35, 3.42 and 2.00, 95 per cent CI: 1.28, 3.14, respectively for low and moderate groups, $p_{trend} < 0.001$) (Table 1).

Time spent outdoors/sports activities was not significantly associated with myopia progression ($\beta = 0.03$, 99 per cent CI: -0.03, 0.08, $p > 0.01$) in six- to 14-year-old children of various ethnicities.[32] While increased outdoor time seems to have a protective effect on incident myopia, this effect may not be pertinent for myopic progression following its initial onset. A recent intervention study has also shown a significant reduction in the rate of incident myopia but not for myopic progression.[48]

A significant limitation of these studies is that outdoor activities were assessed subjectively using questionnaires, rather than an objective measure of light exposure.[20,21,26–32] Precise quantification of time spent outdoors is a major challenge in epidemiological studies. Questionnaires have been widely used but they only provide a subjective measure of time outdoors, are susceptible to recall bias and need to be validated against objective measures. Few studies have used objective measures, such as light meters,[33,34] conjunctival ultraviolet autofluoresence[35,36] (UVAF) and UV dosimeter.[37] A diary recording child activities over a one-week period in conjunction with objective measures of light intensity using a HOBO® pendant light meter may provide more accurate data as the corresponding light intensities could provide a guide to the precision of diary data.[33] Conjunctival UVAF has been used as a bio-marker for outdoor light exposure in Australian young adults[35,36] and is associated with lower myopic prevalence.[37]

Evidence from other studies

In a recent cross-sectional study of 681 Chinese children in Beijing, time spent outdoors was significantly associated with myopia (adjusted OR = 0.32, 95 per cent CI: 0.21, 0.48, $p < 0.001$).[38] Lin and colleagues[39] also observed that Chinese children (n = 370) with low levels of outdoor activity were significantly more myopic (-1.34 ± 2.45 D) than those with moderate (-0.29 ± 2.11 D) and higher levels of outdoor activity (-0.25 ± −2.06 D; $p_{trend} =$ 0.003). In a school-based longitudinal study of five- to 13-year-old Chinese children,[40] outdoor time was negatively correlated with axial elongation ($\beta = -0.12$, 95 per cent CI: -0.15, -0.02, $p = 0.01$) and positively correlated with myopic shift ($\beta = 0.13$, $p = 0.005$) (Table 1); however, the Xichang Pediatric Refractive Error study, which examined 13- to 17-year-old school children in China[41] did not report any association between myopia and outdoor activities (adjusted OR = 1.14, 95 per cent CI: 0.69, 1.89, $p = 0.61$).

There are some potential limitations in this study. Time spent outdoors was self-reported by participants and this may be affected by recall bias. Additionally, 19 per cent of the participants did not complete the survey and the time spent outdoors may have differed between respondents and non-respondents. Thus, these limitations may have resulted in an underestimation of the true association between myopia and time spent outdoors.

There is also substantial evidence that the rate of myopic progression varies across different seasons (Table 2). Fujiwara and colleagues[42] observed that axial length elongation was slower in summer (0.13 ± 0.008 mm) than in winter for Japanese children (0.15 ± 0.01 mm, $p = 0.04$). Similar results were reported for six- to 12-year-old Chinese children[43] with a slower myopic shift (-0.31 ± 0.25 D versus −0.53 ± 0.29 D; $p < 0.001$) and reduced axial elongation in summer than in winter (0.17 ± 0.10 mm versus 0.24 ± 0.09 mm; $p < 0.001$). Danish children with 2,782 ± 19 hours of cumulative available daylight showed less myopia progression and axial elongation (0.26 ± 0.27 D and 0.12 ± 0.09 mm), compared to children with 1681 ± 24 hours of daylight (0.32 ± 0.27 D and 0.19 ± 0.10 mm; $p < 0.01$).[44] This seasonal pattern was also observed in six- to 12-year-old ethnically diverse children from the COMET study,[45] with a slower myopic shift

Author	Study design (location)	Sample size	Age range	Definition of season/ day light hours	Main findings
Fujiwara et al.[42]	Longitudinal (Japan)	92	6 to 12 years	Summer: June-Sep Winter: Dec-Mar	Significantly reduced axial elongation in summer compared to winter:
Donovan et al.[43]	Longitudinal (China)	85	6 to 12	Summer: June-Aug Autumn: Sep-Nov Winter: Dec-Feb Spring: Mar-May	Significantly lower myopia progression and axial elongation in summer compared to other seasons
Cui et al.[44]	Cross-sectional (Denmark)	235	8 to 14 years	Cumulative available daylight hours derived from astronomical tables	Significantly lower myopia progression and axial elongation in children with more available daylight hours compared those with fewer daylight hours
Gwiazda et al.[45]	Longitudinal (United States)	469	6 to 12 years	Winter: Oct-Mar Summer: Apr-Sep	Significantly lower myopia progression and axial elongation in summer compared to winter

Table 2. Evidence for seasonal variations in myopic progression

in summer than in winter (-0.14 ± 0.32 D versus -0.35 ± 0.34 D; $p < 0.0001$). The slower rate of myopic progression in summer could either be due to increased outdoor activity and reduced near work during the school break in summer[46] or may be due to more exposure to daylight or blue light.[47] Both myopic and non-myopic Caucasian children have been shown to spend more time outdoors (21.76 ± 13.80 versus 10.34 ± 6.10 hours per week; $p < 0.001$) and less time studying (1.69 ± 3.71 versus 9.51 ± 6.96 hours per week; $p < 0.001$) during summer break compared to the school year.[46] The light exposure levels among young adults in the United Kingdom were higher in summer than in winter (586.8 ± 89.4 lux versus 209.9 ± 43.0 lux, $p = 0.0002$) with a greater proportion of blue light exposure during summer than in winter[47] (41.3 versus 37.4 per cent; $p < 0.0001$).

Evidence from intervention studies

Few randomised controlled trials have been conducted to assess the effect of structured outdoor programs, as an intervention to increase the time spent outdoors by children and retard myopic incidence and progression[19,48] (Table 3). In the Guangzhou Outdoor Activity Longitudinal study (GOAL),[19] a randomised controlled trial of 1,789 Chinese children aged six to seven years, the two-year incident rate of myopia was significantly lower among children enrolled in an after-school structured outdoor activity (intervention) group compared to a control group (30.4 per cent versus 39.5 per cent, $p < 0.001$). Myopic progression and axial elongation were significantly higher in the control group compared to the intervention group (0.86 ± 0.77 D versus 0.75 ± 0.69 D, $p < 0.01$ and 0.61 ± 0.33 mm versus 0.59 ± 0.33 mm, $p < 0.01$, respectively). Another school-based intervention study involving 571 Chinese Taiwanese children aged seven to 11 years[48] reported a significantly lower incident rate of myopia in children who were in the Recess Outdoor the Classroom (ROC) Program compared to a control group (8.4 versus 17.65 per cent, $p = 0.001$). Myopic progression was significantly lower in the intervention group compared to the control group among non-myopic subjects (-0.25 ± 0.68 D versus -0.39 ± 0.69 D, $p = 0.02$). A proportion of myopic children was also under atropine treatment in both the intervention (~29 per cent) and control (~20 per cent) groups and the outdoor intervention program did not show a combined effect with atropine on myopic progression ($p = 0.85$). The Family Incentive Trial (FIT), a randomised controlled trial of 285 Singapore children estimated time spent outdoors using a questionnaire and a one-week child activities diary, and demonstrated that structured weekend outdoor intervention programs significantly increased outdoor time; 14.75 ± 7.52 hours per week for the intervention group compared to 12.40 ± 6.94 hours per week for the control group, ($p = 0.004$) at six months.[49]

MECHANISMS UNDERLYING THE PROTECTIVE EFFECT

High light levels – evidence from animal studies

Animal studies have shown that light levels as high as 15,000 to 30,000 lux either in the form of artificial laboratory light or natural daylight retard experimental myopia in chicks,[50–53] guinea pigs[54] and monkeys.[55,56] Chicks reared under either light–dark cycles or continuous illumination (50, 500 or 10,000 lux) display increased dopamine concentration for higher luminance levels in both groups.[51] Under both experimental conditions, high light intensity and dopamine concentration were significantly associated with less myopic development (light–dark cycle group: $r = 0.91$, $p < 0.0001$ and continuous light group: $r = 0.74$, $p < 0.0001$).[51] Backhouse, Collins and Phillips[52] showed that chick eyes exposed to continuous lighting of 2,000 lux developed significantly less form deprivation myopia (-4.94 ± 1.21 D) compared to those exposed to continuous lighting of 300 lux (-9.73 ± 0.96 D, $p = 0.022$) or brief periods of 10,000 lux (-9.98 ± 0.85 D; $p = 0.017$). In addition, the intravitreal injection of the dopamine agonist spiperone retards the development of form deprivation myopia.[53] A recent study has shown that drugs that activate D1-like receptors (SKF 38390) inhibit the progression of naturally occurring progressive myopia in albino guinea pigs, whereas activation of D2-like receptors by quinpriole promoted progressive myopia.[54] In monkeys, light intensity as high as 25,000 lux is protective against form deprivation myopia[55] but not against lens-induced myopia.[56]

Based on the results from animal models and epidemiological studies, it is hypothesised that high light levels outdoors or rapid luminance changes[60] trigger the release of dopamine, which is an ocular growth inhibitor,[22,26,27,57–59] which inhibits myopic development.[60]

Author	Study design (location)	Sample size	Age	Type of intervention	Main findings
Morgan et al.[19]	School-based cluster randomised trial (GOAL study †) (China)	1789	6-7 years	Structured outdoor activity outside school hours	Lower incident myopia rate in the intervention group compared to the control group
Wu et al.[48]	Prospective school-based intervention study (Taiwan)	571	7-11 years	Recess outside the classroom (ROC) program to increase outdoor time	Lower incident myopia rate in the intervention group compared to the control group
Ngo et al.[49]	Randomised controlled trial (FIT ‡) (Singapore)	285	6-12 years	Structured weekend outdoor activities, incentives and myopia education	Increased outdoor time in the intervention group compared to the control group

† Guangzhou Outdoor Activity Longitudinal study;
‡ Family Incentive Trial

Table 3. Association between outdoor activity and myopia – evidence from intervention studies

Light chromaticity and spectral composition – evidence from animal studies

There is some evidence that the chromaticity and spectral composition of ambient light may influence myopic inhibition. The longitudinal chromatic aberration of the eye means that not all wavelengths are equally focused on the retina, thus causing reduced contrast of the wavelengths that are focused away from the retina. Hyperopic defocus reduces the contrast of long wavelength components to a greater extent, resulting in a chromatic blur of the retinal image, which could be a guide for the axial elongation of the eye.[61]

The spectral composition of light has a significant impact on ocular growth in guinea pigs.[62–64] Guinea pigs reared in long wavelength light display a significantly more myopic refraction (+1.78 ± 1.22 D) relative to those reared in mixed wavelength light (+3.60 ± 1.65 D) and white light[62] (+5.20 ± 1.67 D, $p < 0.05$). Guinea pigs reared under short wavelength light developed significantly more hyperopia (+6.08 ± 0.80 D) compared to those reared under medium wavelength light (+2.96 ± 0.68 D, $p < 0.01$) and broadband light[63] (+1.36 ± 0.65 D, $p < 0.001$). Vitreous chamber depth was also shorter in guinea pigs raised under blue light (3.23 ± 0.09 mm) compared to those reared under medium wavelength light (3.36 ± 0.10 mm, $p < 0.01$) and broadband light[63] (3.51 ± 0.11 mm, p = 0.0001). Guinea pigs reared in red light developed nearly 2.50 D more myopia ($p < 0.01$) and substantially longer eyes (0.20 mm longer, p = 0.02) compared to those reared under blue light or white light.[64] Rearing guinea pigs under blue light suppresses lens-induced myopia, whereas white light leads to the development of significant myopia.[64]

A similar phenomenon has been observed in chicks with red-green flicker producing increased axial elongation compared to luminance flicker[61] (50 per cent more ocular growth, $p < 0.05$). Altering the chromaticity of ambient light appears to induce and reverse myopia and hyperopia in chicks.[65] In chicks, an excess of red light caused myopia (-2.83 ± 0.25 D), while an excess of blue light caused hyperopia[65] (+4.55 ± 0.21 D). Additionally, red light-induced myopia (-2.21 ± 0.21 D) in chicks could be reversed to hyperopia (+2.50 ± 0.29 D) by changing the excess red light to blue light. Blue light-induced hyperopia (+4.21 ± 0.19 D) could also be reversed to myopia (-1.23 ± 0.12 D) by changing blue light to red light.[65] Together these results suggest that exposure to shorter wavelength blue light is protective against myopia. Since daylight is predominantly composed of blue light, the observed association between time spent outdoors and myopic inhibition in humans may be related to the spectral composition of light.

Increased blood vitamin D levels – evidence from epidemiological and other studies

Exposure to solar ultra violet B radiation (UV-B) outdoors may trigger vitamin D synthesis.[66] In a cross-sectional study of 13- to 25-year-old subjects[67] blood vitamin D levels were inversely related to myopia (β = -3.4, p = 0.005) with myopes having a lower blood level of vitamin D by 3.4 ng/ml compared to non-myopes. Similar results were found among 2,038 adolescents aged 13 to 18 years[68] with a positive association between serum vitamin D levels and refractive error (β = 0.03, 95 per cent CI: 0.00, 0.06, $p < 0.05$). Those with higher levels of serum vitamin D were less likely to have high myopia of 6.00 D or more (adjusted OR = 0.55; 95 per cent CI: 0.34, 0.90; p = 0.02) compared to those with lower serum vitamin D levels. Another cross-sectional study of 946 young Australian adults showed significantly lower serum levels of vitamin D in myopes compared to non-myopes (67.6 nmol versus 72.5 nmol, p = 0.003). Subjects with vitamin D deficiency were more likely to be myopic (adjusted OR = 2.07, 95 per cent CI: 1.29 – 3.32, p = 0.002) compared to those with sufficient levels of vitamin D.[69]

Similarly, in seven- to 15-year-old British children,[70] total vitamin D level was significantly higher in children who spent more time outdoors; however, blood vitamin D levels were not associated with incident myopia after controlling for time outdoors,[70] which suggests that blood vitamin D levels may be a bio-marker for time outdoors. Children who spend more time outdoors may have increased exposure to UV-B radiation and higher blood vitamin D levels.

Vitamin D receptor (VDR) polymorphisms are associated with low to moderate myopia in Whites[71]; however, these polymorphisms were insignificant, when myopia of greater than -4.00 D and other ethnicities were taken into account. Annamaneni and colleagues[72] also found a decreased allele frequency of the *Fok1* VDR gene in high myopes compared to controls, but the *Fok 1* VDR polymorphism was not significantly associated with myopia.

Results from these studies should be interpreted with caution, as these are case-controlled studies with smaller samples than epidemiological studies. Replication studies including larger samples are needed to further confirm the association between these polymorphisms and myopia. Although vitamin D receptor polymorphisms are related to myopia, the functional role of these polymorphisms remains unclear. These associated polymorphisms may be non-functional, resulting in a failure to obtain any consistent associations with refractive error.

It is speculated that increased vitamin D levels secondary to daylight exposure may inhibit myopia by regulating scleral growth through its anti-proliferative effect or it may be important for the functioning of the smooth ciliary muscle involved in accommodation to achieve a clear retinal image both at distance and near.[67,71,72] Increased levels of vitamin D and retinoic acid, an ocular growth regulator, may also be involved in signalling and regulation of the cell cycle;[67,68,71] however, it is difficult to separate the direct effect of vitamin D and vitamin D as a surrogate for outdoor sunlight exposure in human and experimental studies.

Other possible mechanisms underlying the protective effect

The dioptric pattern of the outdoor visual environment may be protective against myopia.[73] In an outdoor visual environment, objects are typically further away with less dioptric variations across the visual scene. Thus, an outdoor visual environment is composed of a more uniform dioptric pattern and subsequently the retinal image has a more uniform pattern of retinal defocus in the periphery compared to indoor viewing conditions, which may influence ocular growth and prevent myopia.[73]

In contrast, objects are much nearer in an indoor visual environment with a higher dioptric value at the point of fixation, which decreases towards the periphery. Thus, an indoor visual environment consists of greater dioptric variations across the visual scene and the retinal image has higher levels of retinal defocus in the periphery that may accelerate ocular growth.[73]

Other mechanisms for the protective effect of time outdoors include an increased depth of focus and retinal image clarity (a reduction in higher-order aberrations) due to pupillary constriction under high light intensity outdoors and a reduced accommodative demand for distance viewing, while in outdoor environments.[26,27,42,46]

ASSOCIATION BETWEEN NEAR WORK AND MYOPIA

Evidence from epidemiological and other studies

Epidemiological studies such as the Orinda Longitudinal Study of Myopia[74] (OLSM), the Singapore Cohort of Risk factors for Myopia[5,6] (SCORM) and the Sydney Myopia Study[75] (SMS) examined the relationship between myopia and near work and have shown equivocal results. Near work appears to be associated with myopia among Caucasian[74] and Australian children[75] but was not significantly associated with incident myopia in Singaporean children.[5,6]

Despite a number of more recent studies investigating the association between myopia and near work, a clear understanding of the nature of this relationship remains elusive, with some studies showing positive findings[21,38,31,40,76–78] and others reporting no relationship[32,39] (Table 4).

In the Beijing Eye Study,[76] a population-based cross-sectional study of 15,066 children aged seven to 18 years, the odds of having myopia was significantly higher in children, who performed prolonged near work (adjusted OR: 1.15; 95 per cent CI: 1.11 to 1.20; $p < 0.001$) and took less rest during studying (adjusted OR: 1.17; 95 per cent CI: 1.13 to 1.21; $p < 0.001$). A school-based study of Chinese school children aged five to 13 years showed that increased reading time was associated with myopia[38] (adjusted OR: 1.38; 95 per cent CI: 1.09 to 1.75; $p = 0.009$) and more axial elongation[40] ($\beta = 0.13$, 95 per cent CI: 0.02 to 0.12, $p = 0.005$). A cross-sectional study of 5,048 Taiwan military conscripts aged 18 to 24 years, showed that increased near work was associated with a more myopic refractive error[77] ($\beta = -0.18$; 95 per cent CI: -0.22 to -0.15; $p < 0.001$) and longer axial length ($\beta = 0.10$, 95 per cent CI: 0.07 to 0.13, $p < 0.01$). In a cross-sectional study of 15,316 Chinese children aged six to 18 years,[78] myopia was significantly associated with increasing levels of near work (adjusted ORs: = 1.14, 95 per cent CI: 1.04 to 1.26; 1.39, 95 per cent CI: 1.24 to 1.56; =1.43, 95 per cent CI: 1.25 to 1.64, for low, moderate and high near work activity, respectively; $p_{trend} < 0.001$) and closer reading

Author	Study design (location)	Sample size	Age range	Definition of near work activity	Main findings
French et al.[21]	Population-based cohort study (Australia)	2103	6 and 12 years	Diopter hours of near work per week	Higher ORs for incident myopia in children with moderate and high levels of near work compared to those with lower levels of near work
Jones-Jordan et al.[29]	Longitudinal cohort (‡CLEERE) (United States)	731	6-14 years	Hours per week on reading, studying and computer work	Significantly higher near work in myopic children compared to emmetropes at myopia onset and 3 years after myopia onset.
Jones-Jordan et al.[31]	Population-based cohort study (United States)	835	6-14 years	Dioptre hours of near work per day	No significant association between dioptre hours of near work and reading
You et al.[76]	Population-based cross-sectional (China)	15,066	7-18 years	Hours of studying per day	Significant association between myopia and longer hours of reading with less frequent breaks
Lee et al.[77]	Cross-sectional (Taiwan)	5048	18-24 years	Hours of near work activities per day	Significant association between myopia and time spent on reading
Gong et al.[78]	Cross-sectional (China)	15,316	6-18 years	Hours of near work activities per day and reading distance	Increasing OR for myopia with increasing near work time and closer reading distances

‡ Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error study

Table 4. Association between near work and myopia – evidence from epidemiological and other studies

distances (adjusted ORs: = 1.39, 95 per cent CI: 1.21 to 1.60; 1.95, 95 per cent CI: 1.24 to 1.69, for 33 cms and more than 33 cms, respectively; $p_{trend} < 0.001$). In a population-based cohort study of incident myopia among 2,103 Australian children aged six and 12 years, six-year-olds with moderate and higher dioptre hours of near work were more likely to become myopic (adjusted ORs: 1.68; 95 per cent CI: 0.89 to 3.16 and 2.35, 95 per cent CI: 1.30 to 4.27, respectively, $p_{trend} < 0.001$) compared to those with lower dioptre hours.[21] Among six- to 14 year-old children from diverse ethnicities, hours spent per week for reading/studying was 0.7 to 1.5 hours more and 0.8 to 1.9 hours more for computer work/video games in children who became myopic compared to emmetropes at the time of onset of myopia and three years after onset of myopia ($p < 0.01$) but not before onset of myopia.[31]

Conversely, several studies have not reported an association between near work and myopia. Near work was not significantly associated with myopia in Chinese children[39] or with myopic progression in children from a diverse ethnic group.[32] The mean myopic refractions were not significantly different between Chinese children with varying levels of near work activity ($p_{trend} = 0.94$ and 0.63, respectively, for primary and secondary school children).[39] Myopia progression did not increase with additional 10 hours of near work in children from varying ethnicities ($\beta = -0.007$, 99 per cent CI: -0.02 to 0.004, $p > 0.01$).[32] Recent evidence suggests that the intensity of near work, that is, sustained reading at closer distance (less than 30 cms) with fewer breaks, may be more important than the total hours of near work[75,76,78]; however, precise quantification of near work is difficult and all studies have used a questionnaire-based approach, which is subjective and may not be reliable.

Possible mechanism - evidence from animal studies

Animal models suggest that retinal image defocus may play a major role in ocular growth and refractive error development in chicks[79–82] and primates.[83–85] Negative lens-induced hyperopic retinal defocus results in axial elongation and myopia, whereas positive lens-induced myopic retinal defocus produces hyperopia.[86] Alterations in the refractive state are accompanied by transient changes in choroidal thickness followed by longer-term changes in scleral ocular growth in both chicks[87,88] and primates.[89,90] Hyperopic defocus causes a rapid thinning of the choroid, thus shifting the retina posteriorly, whereas myopic defocus leads to choroidal thickening, shifting the retina anteriorly to achieve a clear retinal image. In humans, a deficit in the accommodative response (a lag of accommodation), which places the image behind the retina during near work is analogous to the negative lens-induced defocus in animal models. This hyperopic retinal defocus might trigger the growth of the posterior segment to move the retina toward the point of clear focus, leading to axial elongation and myopia. Thus, an individual with a greater lag of accommodation and excessive near work may develop myopia due to hyperopic retinal defocus, which could provide a stimulus for axial elongation.[91–93] Changes in the size of the retinal defocus area or the blur circle size may regulate the release of retinal neuro-modulators that control ocular growth.[94]

ASSOCIATION BETWEEN SEASON OF BIRTH, POST-NATAL LIGHT LEVELS AND MYOPIA

Evidence from epidemiological and other studies

Birth season and post-natal light levels have also been linked to myopia.[95–99] A cross-sectional study including 276,911 Israeli defense subjects aged 16 to 22 years, showed that those born during months with longer daylight hours (12.27 to 13.57 hours and 13.58 to 14.23 hours) were more likely to have moderate myopia (adjusted ORs = 1.06, 95 per cent CI: 1.02, 1.10, $p = 0.002$ and 1.08, 95 per cent CI: 1.04, 1.13; $p = 0.002$, respectively) and high myopia (adjusted ORs = 1.11, 95 per cent CI: 1.03, 1.19; $p = 0.004$ and 1.24, 95 per cent CI: 1.16, 1.33, $p < 0.001$, respectively) compared to those born during months with shorter daylight hours.[95] A cross-sectional study of older British adults reported that subjects born during summer and autumn were more likely to be highly myopic compared to those born in winter[96] (adjusted ORs = 1.17; 95 per cent CI: 1.05, 1.30, $p = 0.006$ and 1.16; 95 per cent CI: 1.04, 1.30, $p = 0.002$, respectively). Similarly, a cross-sectional study of 722 Caucasian infants aged one to three months[97] revealed that 28.5 per cent of infants born during longest daylight hours were myopic, whereas only 17.5 per cent of infants born during shortest daylight hours were myopic ($p = 0.02$). Results from two studies in Finland and China were contradictory[98,99] and did not show any significant trend of increasing myopic prevalence across birth seasons, quartiles of global irradiance or daily hours of darkness during the birth season.[98] These results should be considered with caution, as there may be inaccuracies in the assessment or measurement of refractive error. Vannas and colleagues[98] ascertained myopic status through a questionnaire, whereas other studies[96–99] used non-cycloplegic refraction to measure refractive error, which tends to overestimate myopia due to uncontrolled accommodation in children and young adults. Thus, there may be a random misclassification of myopia that may have caused a spurious association between birth season and myopia.

Possible mechanism - evidence from animal and human studies

Longer photoperiods may influence ocular growth through abnormal diurnal growth rhythms.[100–102] Eyes of young chicks reared under a 12 hour/12 hour light/dark cycle with normal visual experience display an increase in axial length by about 0.13 mm during the day and a decrease of 0.04 mm during the night, whereas in form-deprived eyes axial length increases during both day and night, resulting in myopia primarily due to the inhibition of normal ocular shrinkage observed during the night.[100] Form-deprived chick eyes develop myopia and longer axial lengths, when reared under photoperiods of eight to 18 hours, whereas eyes remain hyperopic with shorter axial length under a photoperiod of 23 hours.[101] These results suggest that chick eyes exhibit a photo period-dependant diurnal growth pattern. Similar diurnal rhythms have also been observed in marmosets.[102] The diurnal growth pattern is age-dependant in marmosets, in which the eyes elongate by 25 μm during the day and decrease in length by 22 μm during the night in juveniles. The reverse is true for adolescents with axial length decreasing by 20 μm during the day and increasing by 38 μm during the night. Choroidal thickness also shows a diurnal rhythm with a decrease during the day and an increase during the night in both juvenile (-12 μm versus +18 μm) and adolescent marmosets (-22 μm versus +21 μm).[102]

Diurnal variations in ocular growth have also been observed in young adults, with the longest axial length and vitreous chamber depth during the day and the shortest during the night. Choroidal thickness also displays diurnal variations opposite in phase to that of axial length, with reduced thickness during the day and increased thickness during the night[103]; however, season of birth is not a good measure of the overall lifetime effect of seasons on refractive error shifts.

ASSOCIATION BETWEEN PARENTAL SMOKING AND MYOPIA

Evidence from epidemiological and other studies

Several studies have shown that parental smoking, in particular maternal smoking during pregnancy, may influence refractive error development in children[104–109] (Table 5).

Parental smoking during a child's lifetime is associated with a lower myopic prevalence,[104] less myopic refraction and shorter axial length compared to those without a history of maternal smoking.[104,105] A recent population-based study of 3,009 Singapore Chinese children aged six to 72 months showed that the ORs for myopia were lower in children with a maternal and paternal history of smoking (adjusted ORs = 0.50, 95 per cent CI: 0.30, 0.84; $p = 0.01$; adjusted OR = 0.72; 95 per cent CI: 0.54, 0.96, $p = 0.02$, respectively) compared to those without.[106] A similar study of children from diverse ethnicities showed that a maternal history of smoking during pregnancy was significantly associated hyperopia greater than 2.00 D (adjusted OR = 1.41; 95 per cent CI: 1.18, 1.69; $p < 0.05$) compared to those who did not have a history of maternal smoking.[107] Another cross-sectional study of 300 Egyptian children aged five to 12 years[108] showed that urine cotinine levels (a biomarker for exposure to tobacco smoke) were significantly higher in hyperopes (64.46 ± 15.82 μg/l) compared to myopes (51.96 ± 18.66 μg/l, $p < 0.0001$) and emmetropes (40.28 ± 15.76 μg/l) ($p < 0.0001$). Conversely, a cross-sectional analysis of a British cohort of 2,487 subjects aged 44 years showed that a maternal history of smoking in early pregnancy was associated with increased risk of high myopia (adjusted relative risks [RRs] = 2.40, 95 per cent CI: 1.10, 5.40, $p < 0.05$) compared to those without a maternal history of smoking.[109] The exact role of parental smoking in myopia development is still unknown. Studies that report a protective association between parental smoking and myopia either did not adjust for[101] or inadequately adjusted for socio-economic status.[104–107] Borchert and colleagues[107] did not adjust for socio-economic status, whereas other studies[104–106] adjusted only for parental education and income. It should be noted that Rahi, Cumberland and Peckham[109] did not control for parental myopia, which is an important risk factor associated with myopia. In addition, there were few high myopes who reported a maternal history of smoking during early pregnancy.

Possible mechanism - evidence from animal studies

Exposure to tobacco smoke may influence ocular growth through nicotine, an important component of cigarette smoke that may influence myopia development through nicotinic acetylcholine receptors.[110,111] The non-selective nicotinic antagonist drugs, namely chlorisondamine and mecamlamine, show the greatest efficacy in inhibiting axial growth and reducing myopic shift in refraction. Two of the nicotinic antagonists (methyllcaconitine and dihydro-β-erythroidine) inhibited myopic growth at high doses but the same effect has not been replicated in low doses, revealing multiphasic dose–response curves.[110] Due to its complex nature of signalling mechanisms, the multiple nicotinic receptor subtypes, differing drug affinities with different receptor subtypes, potential biological effects of other constituents of tobacco smoke, the specific mechanism is yet to be defined.

Although human studies do not provide clear evidence for an association between passive smoking and myopia, animal studies have shown several antagonistic drugs to the neural types of nicotinic acetylcholine receptors which inhibit form-deprivation myopia in chicks.[110,111]

ASSOCIATION BETWEEN BIRTH ORDER AND MYOPIA

Evidence from epidemiological studies

Evidence from epidemiological studies suggests that first-born individuals are more likely to be myopic.[112,113] A meta-analysis of three British cohorts[112] showed that an increase in the number of older siblings was significantly associated with a reduced OR for a visual acuity of 6/12 or worse in both 10- and 11-year-olds (adjusted OR = 0.89; 95 per cent CI: 0.83, 0.94; $p < 0.01$) and 15- and 16-year-old subjects (adjusted OR = 0.84; 95 per cent CI: 0.80, 0.89; $P < 0.01$). A meta-analysis of four population-based cohort studies[113] suggested that first-born subjects were more likely to be myopic compared to non-first-born subjects in the ALSPAC (adjusted OR = 1.31; 95 per cent CI: 1.05, 1.64; $p = 0.016$) and IDFC cohorts (adjusted OR = 1.04, 95 per cent CI: 1.03, 1.06; $p < 0.001$).

Author	Study design (location)	Sample size	Age range	Main findings
Iyer et al.[106]	Population based study (Singapore)	3009	6-72 months	Significantly lower ORs for myopia in children with history of parental smoking during pregnancy compared to those without
El Shazly[108]	Cross-sectional (Egypt)	300	5-12 years	Significantly higher urine cotinine levels in hyperopes compared to myopes
Borchert et al.[107]	Population-based cross-sectional (United States) (MEPEDS and BPEDS†)	9970	6-72 months	Maternal smoking during pregnancy was significantly associated with hyperopia ≥ +2.00D
Rahi et al.[109]	Cohort study (United Kingdom)	2487	44 years	Maternal smoking during early pregnancy was significantly associated with high myopia

† Multi-Ethnic Pediatric Eye Disease and Baltimore Pediatric Eye Disease Studies

Table 5. Evidence for the association between parental smoking and myopia

Despite larger samples, these studies have some limitations. Rudnicka and colleagues[112] classified myopia based on unaided visual acuity, which is not a precise method. The use of non-cycloplegic auto-refraction and subjective refraction to determine refractive error may have overestimated the prevalence or magnitude of myopic refractive error in children and young adults.[113] Thus, there may be a random misclassification of myopia in these studies, which could result in a spurious association between myopia and birth order.

Possible mechanisms

Possible mechanisms underlying the association between birth order and myopia include low birth weight, post-natal catch-up growth and insulin resistance. Most first-born babies tend to have low birth weight for their gestational age compared to second and third-born babies[114,115] and are more likely to have intrauterine growth restraint, which leads to post-natal catch-up growth during the first two years of life.[116–118] Such children are likely to have increased levels of plasma insulin and insulin resistance.[118–120]

High levels of insulin may trigger myopia in a mechanism similar to that observed in chick eyes. Experiments in chicks have shown that intravitreal administration of insulin inhibits positive lens-induced hyperopia and accelerates negative lens-induced axial myopia through the inhibition of choroid thickening, elongation of the anterior chamber and crystalline lens thickening.[121,122]

A large body of evidence shows a trend of increasing educational attainment with decreasing birth order, with first-born children attaining the highest educational level compared to non-first borns.[123–129] Given the link between higher educational level and myopia[74,130–136] and a significant interaction between myopic genetic loci and higher educational level,[137,138] it is likely that myopia is more prevalent in firstborn individuals and education level may be a contributing factor.

ASSOCIATION BETWEEN MATERNAL AGE AND MYOPIA - EVIDENCE FROM EPIDEMIOLOGICAL STUDIES

Maternal age is another important early-life factor associated with myopia. Maternal age greater than 35 years increases the likelihood of varying degrees of myopia (adjusted OR: 1.5, 95 per cent CI: 1.1, 2.0, $p < 0.05$)[109] and reduced unaided distance vision (adjusted OR: 1.10, 95 per cent CI 1.04, 1.17; $p < 0.01$).[112] Maternal age may be linked to myopia as older mothers are more likely to give birth to low birth weight infants[139] and myopia is associated with low birth weight.[109]

CONCLUSION

Population-based data show a consistent protective association between time outdoors and myopia. Results from clinical trials for outdoor intervention programs to reduce incident myopia are promising. Increasing time outdoors during childhood and adolescence could be accomplished through conducting lessons outside the classroom, incorporating outdoor activity in the school curriculum or through structured weekend outdoor programs for families. Evidence for the association of near work with myopia is not as robust as time outdoors and may be difficult to quantify. Experimental models and epidemiological associations suggest a role for neural nicotinic acetylcholine receptors on ocular growth but more studies are warranted.

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