The Effect of Ambient Illuminance on the Development of Deprivation Myopia in Chicks

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Purpose. Recent epidemiologic studies have shown that children who spend a higher proportion of time outdoors are less likely to develop myopia. This study was undertaken to investigate whether light levels may be a relevant factor in the development of myopia.

Methods. Paradigm 1: Chicks were fitted with translucent diffusers for 5 days, with the diffusers removed daily for 15 minutes under one of three lighting conditions: (1) normal laboratory lighting (500 lux), (2) intense laboratory lighting (15,000 lux), or (3) daylight (30,000 lux). A control group, which continuously wore diffusers, was also kept under an illumination of 500 lux. Paradigm 2: Chicks fitted with translucent diffusers were raised for 4 days under one of three lighting conditions: (1) low laboratory lighting (50 lux, $n = 9$), (2) normal laboratory lighting (500 lux, $n = 18$), or (3) intense laboratory lights (15,000 lux, $n = 9$). In groups 1 and 3, the chicks were exposed to either low or high ambient illuminances for a period of 6 hours per day (10 AM–4 PM), but were kept under 500 lux for the remaining time of the light phase. Axial length and refraction were measured at the commencement and cessation of all treatments, with corneal curvature measured additionally in paradigm 2.

Results. Paradigm 1: The chicks exposed daily to sunlight for 15 minutes had significantly shorter eyes (8.81 ± 0.05 mm; $P < 0.01$) and less myopic refractions (−1.1 ± 0.45 D; $P < 0.01$) than did the chicks that had their diffusers removed under normal laboratory light levels (8.98 ± 0.03 mm, −5.3 ± 0.5 D). If the diffusers were removed under intense laboratory lights, the chicks also developed shorter eyes (8.88 ± 0.04 mm; $P < 0.01$) and less myopic refractions (−3.4 ± 0.6D; $P < 0.01$). Paradigm 2: The chicks that wore diffusers continuously under high illuminance had shorter eyes (8.54 ± 0.02 mm; $P < 0.01$) and less myopic refractions (+0.04 ± 0.7D; $P < 0.001$) compared with those chicks reared under normal light levels (8.64 ± 0.06 mm, −5.3 ± 0.9 D). Low illuminance (50 lux) did not further increase deprivation myopia.

Conclusions. Exposing chicks to high illuminances, either sunlight or intense laboratory lights, retards the development of experimental myopia. These results, in conjunction with recent epidemiologic findings, suggest that daily exposure to high light levels may have a protective effect against the development of school-age myopia in children. (*Invest Ophthalmol Vis Sci.* 2009;50:5348–5354) DOI:10.1167/iovs.09-3419

Myopia has become a major public health concern, with prevalence rates rising in several countries, most notably in urban East Asia. There, roughly 80% to 90% of children who are graduating from school are myopic, and ~ 20% have high myopia (< −6 D),[1–3] increasing their risk for chorioretinal diseases.[4,5]

Myopia appears to be both genetically and environmentally determined, with most recent evidence suggesting that it has a multifactorial etiology. There are clearly a small percentage of genetic forms of high myopia, with a number of chromosomal locations reported.[6–14] However, the extremely rapid increase in the prevalence of school myopia world-wide is suggestive of strong environmental influences. More recently, retrospective association studies have suggested that time spent outdoors during childhood is a potent protective factor against the development of myopia.[15–21] Jones et al.,[17] who investigated 514 children in the Orinda Longitudinal Study of Myopia, concluded that greater levels of outdoor activity in the third grade reduced the likelihood that children would have myopia in the eighth grade. They showed that reduced amounts of outdoor activity increases the likelihood that children with two myopic parents will have myopia more so than it does in those children with either no or one myopic parent. Furthermore, the probability that a child with no myopic parents would become myopic was lowest in the children with the highest amount of outdoor activity. More recently, Rose et al.,[16] in a study of 2367 12-year-olds from the Sydney Myopia Study, reported that the children who spent a greater amount of time outdoors had a less myopic and more hyperopic mean refraction, whereas those students who combined high levels of near work with low levels of outdoor activity showed the least hyperopic refraction.

It is presently unclear what factors associated with outdoor activity could protect against the development of myopia. One possibility is the higher levels of ambient illumination experienced outdoors, which constricts the pupil creating greater depth of focus and reducing image blur. Also, the release of the retinal neuromodulator dopamine, a known inhibitor of ocular growth,[22–26] is stimulated by light.[27–31] Another possibility is that increased physical activity outdoors is linked to increased optic flow, causing faster local luminance changes on the retina. Rapid luminance changes were previously proposed to inhibit myopia development.[32] Finally, in children, there is typically less "near work" during outdoor activity, and it could be that this factor also has an inhibitory effect on myopia. Although it is demanding to quantify the distribution of viewing distances and defocus in the fovea and periphery during indoor and outdoor vision in humans, it is relatively easy to test the effects of ambient illuminance and optic flow (generated by self motion) in the animal model of the chicken. Therefore, we have investigated whether ambient illuminance is a factor in the development of experimental myopia in chicks. Furthermore, we have monitored physical activity of the chicks under different illuminances to determine potential effects of differences in optic flow.

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METHODS

Animal Housing

One-day-old male white leghorn chickens were obtained from a local hatchery in Kirchberg, Germany. The chickens were maintained in temperature-controlled rooms under a 12:12 hour light/dark cycle, with incandescent illumination of 500 lux during the light phase, with lights on at 7 AM and off at 7 PM. The chickens had access to unlimited amounts of food and water, and were given 7 days to become accustomed to their surroundings before experiments were commenced. All experiments conformed to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and were approved by the university committee for experiments involving animals.

Experimental Design

Two separate paradigms were investigated in this study. Paradigm 1: The chicks were fitted with translucent diffusers for 5 days, with the diffusers removed daily for 15 minutes under one of three lighting conditions: (1) normal laboratory lighting (500 lux), (2) intense laboratory lighting (15,000 lux), or (3) daylight (30,000 lux), with group sizes of nine chicks per lighting condition. All groups were kept under an ambient illumination of 500 lux outside of the 15 minutes period of diffuser-free vision. A fourth group, which continuously wore diffusers, was also kept under an illumination of 500 lux (control group, $n = 9$). Axial length and refractive measurements were obtained at the commencement and cessation of treatment. Paradigm 2: The chicks were fitted with translucent diffusers and raised for 4 days under one of three lighting conditions; (1) low laboratory lighting (50 lux, $n = 9$), (2) normal laboratory lighting (500 lux, $n = 18$), or (3) intense laboratory lighting (15,000 lux, $n = 9$). In groups 1 and 3, the chicks were exposed to either low or high ambient illuminance for 6 hours per day (10 AM–4 PM), with the animals kept under 500 lux for the remaining period of the light phase. Axial length, refraction, and corneal radius of curvature were measured at the commencement and cessation of treatment.

On the day before treatment, the chicks were anesthetized with diethylether and had a Velcro ring glued to the feathers around the left eye, with the right eye acting as a contralateral control. At the commencement of treatment translucent diffusers were attached to the Velcro mount. In paradigm 1, the diffusers were cleaned each day during the period of diffuser-free vision. In paradigm 2, diffusers were removed briefly at the commencement of the dark phase on day 2 of treatment for cleaning.

Measurement of Ocular Parameters

Refraction, axial length, and corneal curvature were measured by automated infrared photoretinoscopy,[33] A-scan ultrasonography,[34] and infrared photokeratometry without cycloplegia,[35] respectively.

Locomotor Activity

To detect whether there were differences in the activity of the chicks under different ambient illuminances, we used a USB monochrome surveillance camera (640 × 480 pixels, 8-bit gray levels, with a frame rate of 5 Hz) to image the cage from above, with an average chicken being 40 × 40 pixels in size. Software was written in a commercial program (Visual C++ 6.0; Microsoft Corp., Redmond, WA) to record changes in pixel brightness between one video frame and the next at 12,288 equidistant positions in the video frame. Pixel brightness changes that exceeded 30 were considered above pixel noise and were attributed to movements of the chicks. The sum of all pixels that had changed was taken as a measure of the total activity of all the chicks in the cage, with a maximum value of 12,288 and a minimum of 150, which represented the residual pixel noise of the camera, recorded when the cages were empty. The function of the program was verified by waving a hand in the field of view of the camera. The value of the "activity" parameter was proportional to the speed of the hand.

Lighting Design

For "normal laboratory lighting" experiments, the chicks were kept under an illuminance of 500 lux at cage level, as measured by a radiometer (IL1700 Research Radiometer; International Light, Inc., Newburyport, MA), using normal ceiling-mounted triphosphor fluorescent lights (400–to 800 nm, peaking at 530 and 620 nm; Lumi Lux Plus, Voltimum UK, Ltd., London, UK), with a viewing distance of 5 m. For indoor low-light experiments, the chicks were reared in a specially designed cage that reduced the illuminance of the ceiling lights to 50 lux at cage level. The cage reduced the 5 m viewing distance to 60 cm on all but one side. For indoor high-illuminance experiments, the chicks were kept in a specially designed cage with two 1500-W (230-V) quartz-halogen lights (300–1000 nm, peaking at 700 nm) situated 1.5 m above the cage, which provided an illuminance at cage level of 15,000 lux. The 5-m viewing distance within the room was unaffected by the mounting of the high-intensity lights above the cage. For outdoor experiments, the chicks were placed on a balcony, allowing viewing distances up to 10 to 20 m, and exposed to direct sunlight, on full sunny days, at times between 12:30 to 1:00 PM during summer, with an average illuminance of 30,000 lux at cage level. The spectral composition of the sun, at noon, and the quartz-halogen lighting used were very similar over the visible range of the spectrum for the chicks (360–700 nm). This was confirmed using a handheld spectroscope with a digital camera attached to allow analysis of the spectral distribution in ImageJ. The quartz-halogen lights, however, contained a protective UV-absorbing cover glass, which blocked wavelengths below 400 nm.

Statistics

A multivariate analysis of variance (MANOVA), with repeated-measures design, was used to compare pre- and posttreatment values for the measured ocular parameters. A one-way ANOVA, followed by Student's unpaired *t*-test, with Bonferroni correction for multiple testing, was used to analyze between groups posttreatment values for measured ocular parameters. Multivariate ANOVA testing was performed in commercial software (JMP 7.0; SAS. Cary, NC) for analysis of chicken activity.

RESULTS

The Effects of Brief Periods of Normal Vision under Different Ambient Illumination Levels on Ocular Development in Chicks

A repeated-measures MANOVA indicated a significant effect of both diffuser treatment and light intensity, over time, on refractive development ($F = 266.9$, $P < 0.0001$; $F = 21.7$, $P < 0.0001$, respectively) and axial length ($F = 109.0$, $P < 0.0001$; $F = 9.9$, $P < 0.001$, respectively). There was no significant difference in initial refraction ($F = 2.7$, $P = 0.07$), but a small yet significant difference in axial length ($F = 3.1$, $P = 0.03$), between all treatment groups.

The removal of diffusers for a 15-minute period per day under normal laboratory light levels (500 lux), significantly retarded the development of deprivation myopia in comparison to that seen in the chicks reared under 500 lux that did not have their diffusers removed (-5.34 ± 0.49 D, -12.32 ± 0.75; $P < 0.001$, Fig. 1). This protective effect was enhanced if the diffusers were removed for the 15-minute period under intense indoor light (-3.39 ± 0.56 D; $P < 0.001$) and further enhanced if the birds were exposed to direct sunlight (-1.10 ± 0.45 D), compared with chicks exposed to either intense indoor lighting ($P < 0.01$) or normal laboratory light levels ($P < 0.001$). Axial length values corresponded well with refraction, with chicks exposed to 15 minutes of diffuser-free vision under daylight having the shortest eyes (8.81 ± 0.05 mm, $P < 0.01$; Table 1), followed by those exposed to intense

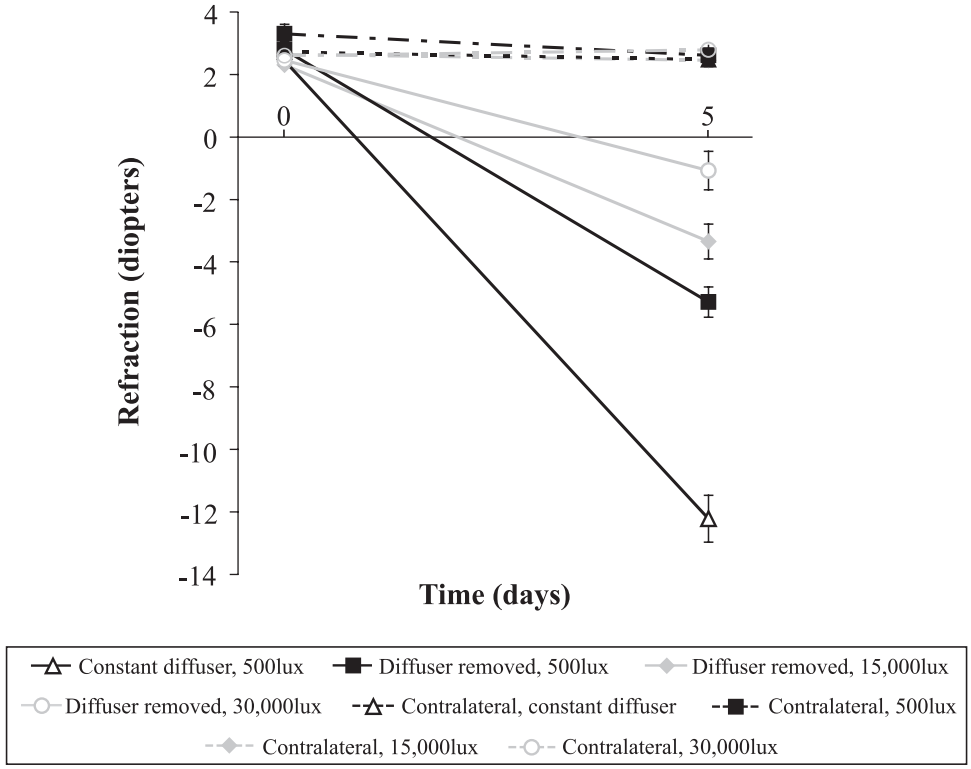

FIGURE 1. Changes in refraction over 5 days of interrupted diffuser wear. Changes in refraction over 5 days in chicks exposed to diffuser-free vision daily, for a period of 15 minutes, under one of three lighting conditions: (1) 500 lux indoors ($n = 9$), (2) 15,000 lux indoors ($n = 9$), or (3) 30,000 lux outdoors ($n = 9$). Changes in refraction are also plotted for an age-matched control group that wore diffusers continuously under an ambient illumination of 500 lux for the 5-day experimental period ($n = 9$).

indoor lighting (8.88 ± 0.04 mm, $P < 0.01$), normal laboratory lighting (8.98 ± 0.03 mm, $P < 0.05$) and finally those which did not have their diffusers removed (9.18 ± 0.16 mm; Table 1). Changes in axial length represented alterations in vitreous chamber depth, with no changes in anterior chamber depth observed (Table 1). Refraction ($F = 1.88$, $P = 0.18$) and axial length ($F = 3.12$, $P = 0.08$) of the contralateral control eyes were unaffected by any treatment regimen.

A MANOVA of the activity level of the chicks, as measured by the change in pixel brightness over time, showed no significant difference between the chicks that had their diffusers removed under normal or intense laboratory lighting (Fig. 2; ANOVA, $P = 0.18$). Of interest, the chicks that wore their diffusers continuously had a higher rate of activity than did those kept under normal or high light during the 15-minute diffuser-free period (ANOVA, $P < 0.001$).

The Effect of Increased Ambient Illumination on the Development of Deprivation Myopia

A MANOVA indicated a significant interactive effect of diffuser treatment and light intensity, over time, on refractive development ($F = 58.8$, $P < 0.0001$; $F = 12.0$, $P < 0.01$, respectively) and axial length ($F = 69.9$, $P < 0.0001$; $F = 11.8$, $P < 0.01$, respectively). There was no significant difference in the initial refraction ($F = 2.25$, $P = 0.10$) or axial length ($F = 2.89$, $P = 0.07$) between the two treatment groups.

The chicks that were fitted with diffusers and raised for 4 days under high indoor light levels (15,000 lux) developed significantly less myopia than those reared under normal lighting conditions (500 lux) in the laboratory (Fig. 3; $P < 0.05$). Correspondingly, the treated eyes from those birds kept under high light levels were significantly shorter than those raised under normal lighting conditions (Table 2; $P < 0.001$). Changes in axial length represented alterations in vitreous chamber depth, with no changes in anterior chamber depth observed. The corneal radius of curvature was unaffected by high light levels over the 4 days of the experiment period compared with those chicks raised under normal light levels (Table 2; $P = 0.52$). Refraction ($F = 0.3$, $P = 0.60$), axial length ($F = 0.4$, $P = 0.52$), and corneal radius of curvature ($F = 0.6$, $P = 0.46$) were unaffected in the contralateral control eye of the chicks exposed to high light levels compared with the contralateral values obtained from the birds raised under normal light conditions.

TABLE 1. Changes in Ocular Parameters over 5 Days of Interrupted Diffuser Wear

Treatment	LI (lux)	RE (D), Day 0	RE (D), Day 5	AC (mm), Day 0	AC (mm), Day 5	AL (mm), Day 0	AL (mm), Day 5
Constant diffuser wear	500	2.44 ± 0.11	−12.32 ± 0.75	0.88 ± 0.01	0.91 ± 0.02	8.22 ± 0.01	9.18 ± 0.16
Diffuser removed	500	2.79 ± 0.26	−5.34 ± 0.49	0.87 ± 0.03	0.90 ± 0.03	8.15 ± 0.02	8.98 ± 0.03
Diffuser removed	15,000	2.31 ± 0.07	−3.39 ± 0.56	0.88 ± 0.02	0.89 ± 0.02	8.26 ± 0.02	8.88 ± 0.04
Diffuser removed	30,000	2.45 ± 0.49	−1.10 ± 0.45	0.89 ± 0.02	0.91 ± 0.01	8.13 ± 0.12	8.81 ± 0.05
Contralateral, constant diff.	500	2.72 ± 0.10	2.48 ± 0.23	0.90 ± 0.03	0.90 ± 0.02	8.23 ± 0.01	8.56 ± 0.02
Contralateral, diff. removed	500	3.31 ± 0.31	2.62 ± 0.23	0.87 ± 0.04	0.92 ± 0.02	8.15 ± 0.02	8.56 ± 0.03
Contralateral, diff. removed	15,000	2.64 ± 0.22	2.45 ± 0.12	0.89 ± 0.02	0.90 ± 0.03	8.23 ± 0.02	8.53 ± 0.03
Contralateral, diff. removed	30,000	2.60 ± 0.69	2.79 ± 0.50	0.89 ± 0.01	0.91 ± 0.03	8.14 ± 0.09	8.58 ± 0.05

LI, light intensity; RE, refraction; AC, anterior chamber depth; AL, axial length.

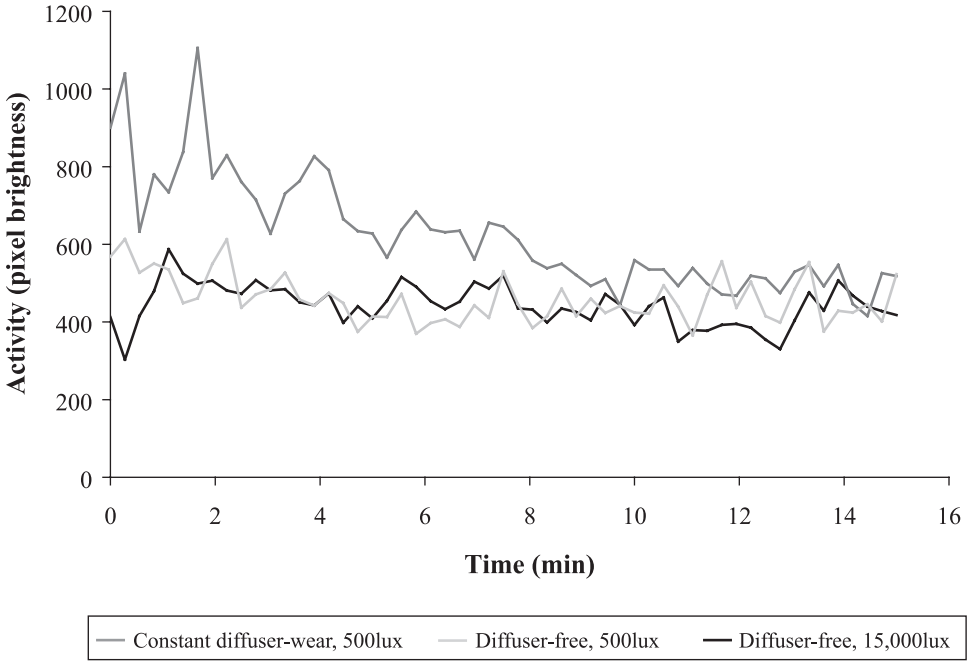

FIGURE 2. Measurement of chicken activity under normal and high ambient illuminance. Changes in chicken activity over a 15 minutes period under one of three experimental conditions: (1) diffuser removed under an illumination of 500 lux ($n = 9$), (2) diffuser removed under an illumination of 15,000 lux ($n = 9$), or (3) continuous diffuser-wear under an illumination of 500 lux ($n = 9$).

The Effect of Reduced Ambient Illumination on the Development of Deprivation Myopia

A MANOVA indicated a significant interaction between diffuser treatment, over time, on refractive development ($F = 96.2$, $P < 0.0001$) and axial length ($F = 115.9$, $P < 0.0001$). No interaction between light levels, over time, and refraction ($F = 0.01$, $P = 0.9$) or axial length ($F = 1.5$, $P = 0.2$) was detected. There were no significant differences in the initial refraction ($F = 1.4$, $P = 0.26$) or axial length ($F = 1.4$, $P = 0.25$) between any of the treatment groups.

Chicks fitted with translucent diffusers and raised for 4 days under low illuminance (50 lux) developed similar amounts of myopia to those chicks reared under normal lighting conditions (Fig. 3; $P = 0.90$). Correspondingly, there was no statistically significant difference between the axial length (Table 2; $P = 0.23$) or corneal radius of curvature ($P = 0.58$) of treated eyes from the birds kept under low and normal illuminance levels. Refraction ($P = 0.81$), axial length ($P = 0.06$), and corneal radius of curvature ($P = 0.94$) were unaffected in the contralateral control eyes of the chicks exposed to low light levels (Table 2).

DISCUSSION

In the present study, exposure to high ambient illumination, either sunlight or intense laboratory lights, retarded the development of deprivation myopia in chicks. More specifically, the removal of diffusers for 15 minutes per day retarded the development of myopia by roughly 50%, as has been previously shown.[36] This protective effect was significantly enhanced if the diffusers were removed under high illumination levels, produced by exposure to either direct sunlight or high-inten-

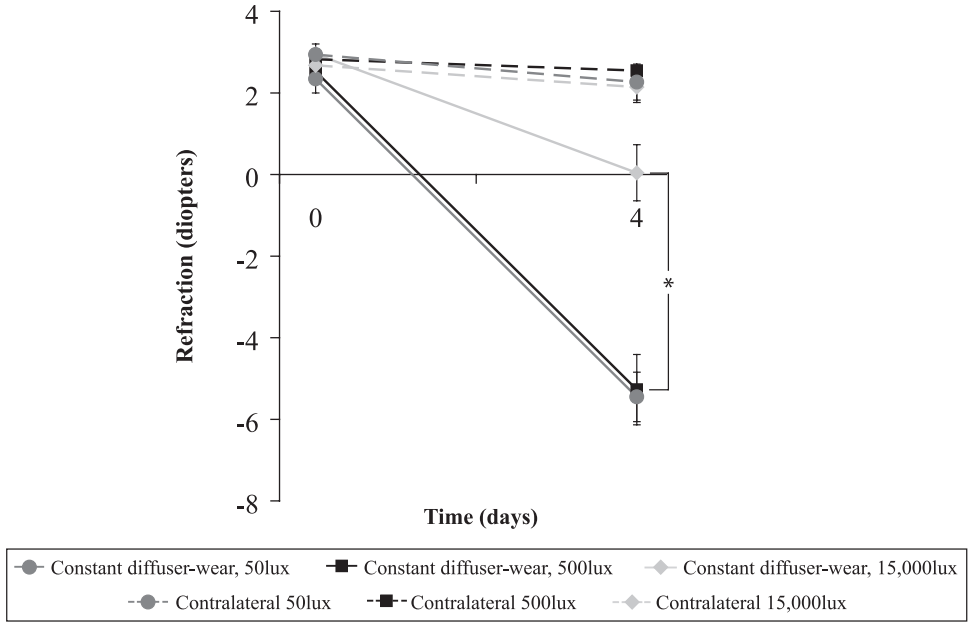

FIGURE 3. The effect of ambient illuminance on refractive development in chicks which wore their diffusers continuously. Changes in refraction over 4 days in chicks fitted with diffusers and raised under one of three illuminances: (1) 50 lux ($n = 9$), (2) 500 lux (control group, $n = 18$), or (3) 15,000 lux ($n = 9$). Groups 1 and 3 were exposed to either 50 lux or 15,000 lux for a period of 6 hours per day, between 10 AM and 4 PM, with the animals being reared under an ambient illumination of 500 lux for the remaining period of the light phase.

Table 2. The Effect of Ambient Illuminance on Ocular Development in Chicks Wearing Diffusers

Treatment	LI (lux)	RE (D), Day 0	RE (D), Day 4	AC (mm), Day 0	AC (mm), Day 4	AL (mm), Day 0	AL (mm), Day 4	CC (mm), Day 0	CC (mm), Day 4
Constant diffuser	50	2.34 ± 0.35	−5.45 ± 0.61	0.88 ± 0.02	0.90 ± 0.02	8.06 ± 0.02	8.61 ± 0.02	3.10 ± 0.02	3.24 ± 0.02
Constant diffuser	500	2.53 ± 0.14	−5.27 ± 0.86	0.89 ± 0.01	0.88 ± 0.02	8.18 ± 0.02	8.64 ± 0.06	3.12 ± 0.03	3.31 ± 0.05
Constant diffuser	15,000	2.95 ± 0.12	0.04 ± 0.69	0.89 ± 0.02	0.90 ± 0.02	8.20 ± 0.01	8.54 ± 0.02	3.12 ± 0.02	3.26 ± 0.03
Contralateral, constant diff.	50	2.94 ± 0.26	2.27 ± 0.44	0.89 ± 0.02	0.89 ± 0.01	8.06 ± 0.02	8.20 ± 0.02	3.10 ± 0.02	3.23 ± 0.01
Contralateral, constant diff.	500	2.86 ± 0.12	2.73 ± 0.12	0.88 ± 0.02	0.90 ± 0.02	8.21 ± 0.02	8.44 ± 0.05	3.13 ± 0.03	3.24 ± 0.02
Contralateral, constant diff.	15,000	2.82 ± 0.17	2.55 ± 0.11	0.90 ± 0.02	0.89 ± 0.03	8.22 ± 0.02	8.41 ± 0.02	3.13 ± 0.03	3.27 ± 0.03

LI, light intensity; RE, refraction; AC, anterior chamber depth; AL, axial length; CC, corneal radius of curvature.

sity indoor lights. Likewise, the rearing of chicks fitted with translucent diffusers under high indoor illumination for 6 hours per day significantly retarded the development of deprivation myopia, whereas, rearing chicks with diffusers under low light (50 lux) for 6 hours per day did not induce more myopia than that seen in the chicks raised under normal laboratory light (500 lux).

Recent epidemiologic findings have suggested that time spent outdoors as a child has a protective effect against the development of myopia.[15–21] In a study of 514 children from the Orinda Longitudinal Study of Myopia, Jones et al.[17] reported that lower levels of sport or outdoor activity and having myopic parents were the strongest nonocular predictors for the development of school-age myopia. Similarly, several recent epidemiologic studies have reported an inverse relationship between school-aged myopia development and outdoor activity[20] or sports.[15,20] In another study, Rose et al.,[16] specifically addressed the relationship between outdoor activity and the prevalence of myopia in children and reported an inverse relationship between high levels of total time spent outdoors (as opposed to time spent playing sports, per se, as reported in earlier studies) and the development of myopia, with the children who spent the greatest time outdoors in conjunction with low levels of near-work showing the least myopic and most hyperopic mean refraction. As they discussed, one may argue that increased time spent outdoors simply reduces the time engaged in near work, which has been postulated as a possible myopigenic factor. However, they observed no correlation between near work or midrange working activities and refraction. Similarly, in a study of Turkish medical students, Onal et al.[18] found no correlation between close work and development of myopia, whereas outdoor activity during childhood was found to be protective against it. Our current findings suggest that the protective effect afforded to children by outdoor activity is light-intensity driven.

The current findings indicate that it is not exposure to sunlight per se that protects against the development of myopia, but rather the intensity of the illumination, as brief periods of exposure to high-intensity halogen-quartz lamps, with a spectral distribution of 300 to 1000 nm, peaking at 700 nm, significantly retarded the development of experimental myopia (~60%). The stronger retardation of myopia produced by exposure to sunlight is likely the result of the greater intensity of its illumination, rather than any specific properties associated with the sun's spectrum, as the spectral distribution of the halogen lights currently used are similar to that of daylight over the range of visible light for chickens (360–700 nm).[37,38] It should be noted, however, that the halogen lights did not produce light in the UV range. Therefore, we cannot exclude the possibility that the greater effect of sunlight was associated with its UV component, rather than the difference in illuminance. Because of the similar spectrum of sunlight and the halogen lights between 400 and 700 nm, we did not discern in the present study any interactions between the intensity and the spectral composition of the light source in the protective effects afforded the chicks against the development of myopia. This question requires further investigation, as the spectral composition of sunlight varies with geographical location, time of day, and season. Also, recent animal studies have suggested that although chromatic contrast is not essential for lens compensation and emmetropization in chicks,[39–41] the two components of lens compensation (vitreous chamber depth and choroidal thickness) are affected differentially by monochromatic illumination.[41] The current findings, however, suggest that ultraviolet (UV) input is not required for the retardation of myopia development, as the quartz-halogen lights presently used do not emit wavelengths in the UV range. Supporting this hypothesis, Rohrer et al.[39] have reported that chicks are unable to compensate for imposed optical defocus when reared under near-UV light. Histologic analysis of the sampling intervals for the UV receptors indicated that their spatial resolving power was too low to detect defocus,[39] suggesting that this system is not vital to the visually guided emmetropization process.

Rearing chicks under high illuminances for 6 hours per day (10 AM–4 PM), for a period of 4 days, significantly retarded the development of deprivation myopia, whereas the same time protocol applied to low illuminances did not enhance the development of deprivation myopia. Similar observations were reported by Feldkaemper et al.[42] and Moore et al. (*IOVS* 1998; 39:ARVO E-Abstract 3281), in which the ocular development of chicks fitted with neutral-density filters of between 0.5 to 1, were unaffected, suggesting that low illuminance itself is not a stimulant for myopic growth. This finding suggests that the effect of light intensity on myopia's development is not a linear response, but rather that there are specific interactions between ambient illumination and ocular growth at higher intensities. However, it should be noted that at illumination levels significantly lower then those used presently, produced by ND filters of between 2 and 3, both Feldkaemper et al.[42] and Moore et al. (*IOVS* 1998;39:ARVO E-Abstract 3281) observed the development of myopia. Such myopic growth appears to be related to unilateral reductions in illumination levels, as this effect could not be reproduced if the ambient illumination level was reduced by 2 log units.[42] It should be noted, however, that investigators in earlier studies examining the long-term consequences (weeks–months) of dim-light rearing (<1 lux) observed significant ocular enlargement in chicks, without an accompanying flattening of the cornea, suggestive of myopia development, although refractive measurements were not obtained.[43–45] Such findings suggest that diurnal rearing of chicks in light levels significantly below those used presently,

for extended periods (months), can induce ocular enlargement.

The question remains, how does exposure to high ambient illumination protect against the development of myopia? One possibility, investigated presently, is that higher illuminance levels lead to elevated levels of physical activity in chicks, creating greater optic flow and hence faster local luminance changes on the retina. Rapid luminance changes were previously proposed to inhibit myopia development.[32] However, we observed no difference in the activity of chicks exposed to 15 minutes of diffuser-free vision under either high or normal ambient illumination, instead, chicks that did not have their diffusers removed in this 15 minutes period showed the highest level of activity, as measured by changes in pixel brightness over time.

Recent animal findings may suggest that high illuminance levels retard the development of experimental myopia via corneal flattening. Cohen et al.[46] have reported a correlation between light intensity and corneal power in chicks exposed to continuous illumination. Specifically, the higher the illumination level under which the chicks were raised the greater the flattening of the cornea observed and the amount of hyperopia that developed. Their results suggest that the effects of continuous illumination on ocular development are intensity dependent. However, we observed no changes in the corneal radius of curvature in chicks exposed to high light levels over a period of 4 days under light/dark cyclic conditions, compared with those chicks exposed to either 500 or 50 lux. Similar findings have been reported by Lauber and Kinnear,[47] in which chicks raised under bright light (100-W incandescent light bulb) or dim light (7.5-W incandescent light bulb) showed no significant differences in corneal radius of curvature. Further, a study by Blatchford et al.[48] reported no significant changes in corneal radius of curvature between chicks raised under one of three lighting conditions (5, 50, or 500 lux) during the photoperiod, over a 5-week period. These results suggest that the light intensity–dependent changes in corneal radius of curvature are a specific phenomenon associated with continuous illumination, most likely related to the loss of diurnal and/or circadian rhythms, particularly in the expression of the neuromodulators melatonin and dopamine. Supporting this hypothesis, Li and Howland[49] have shown that a diurnal light–dark rhythm presented to one of the three photosensitive organs (the pineal gland and both eyes) in chicks can protect the eyes from the effects of constant illumination—namely, corneal flattening, anterior chamber thinning and vitreous chamber deepening.[49–52]

An alternative hypothesis is that higher illumination levels lead to pupil constriction, providing greater depth of focus and reduced image blur, with Schaeffel et al.[53] reporting that the pupil size in chicks is already reduced by roughly 50% of its maximum diameter under an illuminance of 1,000 lux. This hypothesis may provide an explanation for the protective effect afforded by higher illuminance levels to the chicks that experienced 15 minutes of diffuser-free vision, as greater depth of focus, and hence less image blur, may provide a stronger stop-growth signal. However, this hypothesis does not explain how increased illumination retarded the development of myopia in the chicks that wore diffusers continuously, as a greater depth of focus and hence a reduction in the amount of image blur cannot occur under the diffusers. It should also be noted that pupil constriction in bright light had no effect on emmetropization in the uncovered fellow eyes.

Alternatively, exposure to increased illumination may induce the release of neuromodulators such as dopamine, a known inhibitor of ocular growth, whose release from the dopaminergic amacrine cells is light sensitive.[27–31] In chicks and monkeys, the diurnal release of dopamine is disrupted during the development of deprivation myopia,[54,55] with Weiss and Schaeffel[55] observing a 30% reduction in daytime retinal dopamine levels during the development of deprivation myopia. Further, the intravitreous injection of such dopamine agonists as apomorphine,[22–25] 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide (ADTN),[26,56] and quinpirole[26] retards the development of FDM, implying a role for dopamine in the modulation of eye growth. More recently, McCarthy et al.[26] have shown that the ability of brief periods of diffuser-free vision to retard the development of deprivation myopia is blocked by the intravitreous injection of dopamine antagonists. In addition, the authors showed that placing chicks in the dark during the period of diffuser-free vision abolishes this protective effect, but is restored if dopamine agonists are injected immediately before dark treatment. These findings demonstrate that the ability of brief periods of normal vision to retard the development of deprivation myopia is partially driven by changes in dopamine signaling.

One may postulate, based on the current findings, that dopamine release in the chick retina has a graded response to increasing illumination, above a specific intensity threshold, and hence the higher the illumination level the greater the retardation of myopic growth. Supporting this hypothesis, Brainard and Morgan[29] have reported that dopamine synthesis in the rat retina displays a graded response to increasing irradiances of white light (6–170 lux), with illuminance levels of 170 lux, or greater, eliciting a maximum response.

Conclusions

The development of FDM in chicks can be significantly retarded by exposing animals to higher levels of ambient illumination produced by exposure to either direct sunlight or intense indoor lights. The current findings suggest that the apparent protective effect afforded to children by time outdoors, reported in several recent epidemiologic studies, can be explained, in part, by exposure to higher ambient illuminances. In general, the results of this study may suggest that children who are exposed daily to high ambient illuminances, as experienced by spending time outdoors, are less likely to develop school-age myopia.

References

1. Lin LL, Shih YF, Hsiao CK, Chen CJ. Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. *Ann Acad Med* (*Singapore*). 2004;33:27–33.
2. Saw SM, Wu HM, Seet B, et al. Academic achievement, close up work parameters, and myopia in Singapore military conscripts. *Br J Ophthalmol.* 2001;85:855–860.
3. Morgan I, Rose K. How genetic is school myopia? *Prog Retin Eye Res.* 2005;24:1–38.
4. Saw SM. How blinding is pathological myopia? *Br J Ophthalmol.* 2006;90:525–526.
5. Saw SM, Gazzard G, Shih-Yen EC, Chua WH. Myopia and associated pathological complications. *Ophthalmic Physiol Opt.* 2005;25:381–391.
6. Schwartz M, Haim M, Skarsholm D. X-linked myopia: Bornholm eye disease—linkage to DNA markers on the distal part of Xq. *Clin Genet.* 1990;38:281–286.
7. Young TL, Ronan SM, Drahozal LA, et al. Evidence that a locus for familial high myopia maps to chromosome 18p. *Am J Hum Gen.* 1998;63:109–119.
8. Farbrother JE, Kirov G, Owen MJ, Pong-Wong R, Haley CS, Guggenheim JA. Linkage analysis of the genetic loci for high myopia on 18p, 12q, and 17q in 51 U.K. families. *Invest Ophthalmol Vis Sci.* 2004;45:2879–2885.
9. Naiglin L, Gazagne C, Dallongeville F, et al. A genome wide scan for familial high myopia suggests a novel locus on chromosome 7q36. *J Med Genet.* 2002;39:118–124.

10. Paluru P, Ronan SM, Heon E, et al. New locus for autosomal dominant high myopia maps to the long arm of chromosome 17. *Invest Ophthalmol Vis Sci.* 2003;44:1830–1836.
11. Stambolian D, Ibay G, Reider L, et al. Genomewide linkage scan for myopia susceptibility loci among Ashkenazi Jewish families shows evidence of linkage on chromosome 22q12. *Am J Hum Genet.* 2004;75:448–459.
12. Hammond CJ, Andrew T, Mak YT, Spector TD. A susceptibility locus for myopia in the normal population is linked to the PAX6 gene region on chromosome 11: a genomewide scan of dizygotic twins. *Am J Hum Genet.* 2004;75:294–304.
13. Zhang Q, Guo X, Xiao X, Jia X, Li S, Hejtmancik JF. A new locus for autosomal dominant high myopia maps to 4q22–q27 between D4S1578 and D4S1612. *Mol Vis.* 2005;11:554–560.
14. Nallasamy S, Paluru PC, Devoto M, Wasserman NF, Zhou J, Young TL. Genetic linkage study of high-grade myopia in a Hutterite population from South Dakota. *Mol Vis.* 2007;13:229–236.
15. Khader YS, Batayha WQ, Abdul-Aziz SM, Al-Shiekh-Khalil MI. Prevalence and risk indicators of myopia among schoolchildren in Amman, Jordan. *East Mediterr Health J.* 2006;12:434–439.
16. Rose KA, Morgan IG, Ip J, et al. Outdoor activity reduces the prevalence of myopia in children. *Ophthalmology.* 2008;115:1279–1285.
17. Jones LA, Sinnott LT, Mutti DO, Mitchell GL, Moeschberger ML, Zadnik K. Parental history of myopia, sports and outdoor activities, and future myopia. *Invest Ophthalmol Vis Sci.* 2007;48:3524–3532.
18. Onal S, Toker E, Akingol Z, et al. Refractive errors of medical students in Turkey: one year follow-up of refraction and biometry. *Optom Vis Sci.* 2007;84:175–180.
19. Rose KA, Morgan IG, Smith W, Burlutsky G, Mitchell P, Saw SM. Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney. *Arch Ophthalmol.* 2008;126:527–530.
20. Mutti DO, Mitchell GL, Moeschberger ML, Jones LA, Zadnik K. Parental myopia, near work, school achievement, and children's refractive error. *Invest Ophthalmol Vis Sci.* 2002;43:3633–3640.
21. Parssinen O, Lyyra AL. Myopia and myopic progression among schoolchildren: a three-year follow-up study. *Invest Ophthalmol Vis Sci.* 1993;34:2794–2802.
22. Stone RA, Lin T, Laties AM, Iuvone PM. Retinal dopamine and form-deprivation myopia. *Proc Natl Acad Sci U S A.* 1989;86:704–706.
23. Iuvone PM, Tigges M, Stone RA, Lambert S, Laties AM. Effects of apomorphine, a dopamine receptor agonist, on ocular refraction and axial elongation in a primate model of myopia. *Invest Ophthalmol Vis Sci.* 1991;32:1674–1677.
24. Rohrer B, Spira AW, Stell WK. Apomorphine blocks form-deprivation myopia in chickens by a dopamine D2-receptor mechanism acting in retina or pigmented epithelium. *Vis Neurosci.* 1993;10:447–453.
25. Schmid KL, Wildsoet CF. Inhibitory effects of apomorphine and atropine and their combination on myopia in chicks. *Optom Vis Sci.* 2004;81:137–147.
26. McCarthy CS, Megaw P, Devadas M, Morgan IG. Dopaminergic agents affect the ability of brief periods of normal vision to prevent form-deprivation myopia. *Exp Eye Res.* 2007;84:100–107.
27. Besharse JC, Iuvone PM. Is dopamine a light-adaptive or a dark-adaptive modulator in retina? *Neurochem Int.* 1992;20:193–199.
28. Boelen MK, Boelen MG, Marshak DW. Light-stimulated release of dopamine from the primate retina is blocked by 1–2-amino-4-phosphonobutyric acid (APB). *Vis Neurosci.* 1998;15:97–103.
29. Brainard GC, Morgan WW. Light-induced stimulation of retinal dopamine: a dose-response relationship. *Brain Res.* 1987;424:199–203.
30. Boatright JH, Hoel MJ, Iuvone PM. Stimulation of endogenous dopamine release and metabolism in amphibian retina by light- and K+-evoked depolarization. *Brain Res.* 1989;482:164–168.
31. Kolbinger W, Weiler R. Modulation of endogenous dopamine release in the turtle retina: effects of light, calcium, and neurotransmitters. *Vis Neurosci.* 1993;10:1035–1041.
32. Schwahn HN, Schaeffel F. Flicker parameters are different for suppression of myopia and hyperopia. *Vision Res.* 1997;37:2661–2673.
33. Schaeffel F, Hagel G, Eikermann J, Collett T. Lower-field myopia and astigmatism in amphibians and chickens. *J Opt Soc Am.* 1994;11:487–495.
34. Schaeffel F, Howland HC. Properties of the feedback loops controlling eye growth and refractive state in the chicken. *Vision Res.* 1991;31:717–734.
35. Schaeffel F, Howland HC. Corneal accommodation in chick and pigeon. *J Comp Physiol.* 1987;160:375–384.
36. Napper GA, Brennan NA, Barrington M, Squires MA, Vessey GA, Vingrys AJ. The duration of normal visual exposure necessary to prevent form deprivation myopia in chicks. *Vision Res.* 1995;35:1337–1344.
37. van Norren D. Two short wavelength sensitive cone systems in the pigeon, chicken and daw. *Vision Res.* 1975;15:1164–1166.
38. Wortel JF, Rugenbrink H, Nuboer JFW. The photopic spectral sensitivity of the dorsal and ventral retina of the chicken. *J Comp Physiol.* 1987;A160:151–154.
39. Rohrer B, Schaeffel F, Zrenner E. Longitudinal chromatic aberration and emmetropization: results from the chicken eye. *J Physiol.* 1992;449:363–376.
40. Wildsoet CF, Howland HC, Falconer S, Dick K. Chromatic aberration and accommodation: their role in emmetropization in the chick. *Vision Res.* 1993;33:1593–1603.
41. Rucker FJ, Wallman J. Cone signals for spectacle-lens compensation: differential responses to short and long wavelengths. *Vision Res.* 2008;48:1980–1991.
42. Feldkaemper M, Diether S, Kleine G, Schaeffel F. Interactions of spatial and luminance information in the retina of chickens during myopia development. *Exp Eye Res.* 1999;68:105–115.
43. Lauber JK, Oishi T. Lid suture myopia in chicks. *Invest Ophthalmol Vis Sci.* 1987;28:1851–1858.
44. Bercovitz AB, Harrison PC, Leary GA. Light induced alterations in growth pattern of the avian eye. *Vision Res.* 1972;12:1253–1259.
45. Harrison PC, Bercovitz AB, Leary GA. Development of eye enlargement of domestic fowl subjected to low intensity light. *Int J Biometeorol.* 1968;12:351–358.
46. Cohen Y, Belkin M, Yehezkel O, Avni I, Polat U. Light intensity modulates corneal power and refraction in the chick eye exposed to continuous light. *Vision Res.* 2008;48:2329–2335.
47. Lauber JK, Kinnear A. Eye enlargement in birds induced by dim light. *Can J Ophthalmol.* 1979;14:265–269.
48. Blatchford RA, Klasing KC, Shivaprasad HL, Wakenell PS, Archer GS, Mench JA. The effect of light intensity on the behavior, eye and leg health, and immune function of broiler chickens. *Poultry Sci.* 2009;88:20–28.
49. Li T, Howland HC. The effects of constant and diurnal illumination of the pineal gland and the eyes on ocular growth in chicks. *Invest Ophthalmol Vis Sci.* 2003;44:3692–3697.
50. Li T, Troilo D, Glasser A, Howland HC. Constant light produces severe corneal flattening and hyperopia in chickens. *Vision Res.* 1995;35:1203–1209.
51. Guo SS, Sivak JG, Callender MG, Herbert KL. Effects of continuous light on experimental refractive errors in chicks. *Ophthalmic Physiol Opt.* 1996;16:486–490.
52. Li T, Howland HC. Modulation of constant light effects on the eye by ciliary ganglionectomy and optic nerve section. *Vision Res.* 2000;40:2249–2256.
53. Schaeffel F, Howland HC, Farkas L. Natural accommodation in the growing chicken. *Vision Res.* 1986;26:1977–1993.
54. Iuvone PM, Tigges M, Fernandes A, Tigges J. Dopamine synthesis and metabolism in rhesus monkey retina: development, aging, and the effects of monocular visual deprivation. *Vis Neurosci.* 1989;2:465–471.
55. Weiss S, Schaeffel F. Diurnal growth rhythms in the chicken eye: relation to myopia development and retinal dopamine levels. *J Comp Physiol A.* 1993;172:263–270.
56. Ashby R, McCarthy CS, Maleszka R, Megaw P, Morgan IG. A muscarinic cholinergic antagonist and a dopamine agonist rapidly increase ZENK mRNA expression in the form-deprived chicken retina. *Exp Eye Res.* 2007;85:15–22.