Environmental Influences on Myopia

Donald O. Mutti, OD, PhD, FAAO

Financial Disclosures

• Received honorarium from Welch Allyn for service on scientific advisory panel
• Received grant funding from Johnson & Johnson Vision Care

Collaborators

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University of Houston College of Optometry

J. Daniel Twelker
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The CLEERE Study Group

Objectives

• Make the case that although myopes do more near work, near work plays no causative role in risk of onset or rate of progression.

• Myopes spend less time outdoors. More time outdoors is protective against onset but does not affect the rate of progression.

• Show how pupil testing may be an effective probe of retinal release of dopamine that may be the basis of the beneficial effect of time outdoors.
**Increase in Prevalence with Time?**

- Graph showing prevalence of myopia (%)
- Data points for United States (US) and Taiwan

**Orinda Longitudinal Study of Myopia**

- Community-based volunteer sample
- Children measured in the schools
- Over 1,500 children age 6-14 enrolled
- Begun in 1989
- First study to measure all the major optical ocular components
- Became CLEERE, 4,929 children across US for ethnic diversity

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**Orinda Longitudinal Study of Myopia**

- Cycloplegic autorefration (tropicamide 1%)
- Phakometry for crystalline lens radii
- Ultrasound for axial dimensions
  - Anterior chamber depth
  - Lens thickness
  - Vitreous chamber depth
  - Axial length
- Corneal topography
- Environmental exposures
- Parental history
“Those who do much close work in their youth become myopic.”

Near Work—Cohn (1886)
*The Hygiene of the Eye in Schools*

- 1% of 240 village schoolchildren were myopic
- 13% to 60% of 361 city schoolchildren were myopic

Young et al. (1969)
*The Eskimo Study*

- Average refractive error of 238 Eskimo children aged 6-25 years = −0.12 D
- Average refractive error of 225 Eskimo adults over age 25 years = +1.45 D
- 43.3% of children more myopic than −0.25 D
- 13.8% of young adults more myopic than −0.25 D
Accommodative Lag in Myopes
Gwiazda et al. (1993)

Orinda Longitudinal Study of Myopia
- community-based volunteer sample
- children measured in the schools
- over 1,500 children age 6-14 enrolled
- begun in 1989
- first study to measure all the major optical ocular components
- became CLEERE: 4,929 children across US for ethnic diversity by 2010
Cross-sectional Near Work and Prevalence, Score: 10/15

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Odds Ratio (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murugan</td>
<td>2000</td>
<td>1.89 (1.01, 3.50)</td>
<td>4.96</td>
</tr>
<tr>
<td>Saw</td>
<td>2001</td>
<td>2.00 (1.93, 2.80)</td>
<td>0.76</td>
</tr>
<tr>
<td>Muth</td>
<td>2002</td>
<td>1.02 (1.01, 1.93)</td>
<td>50.10</td>
</tr>
<tr>
<td>Saw</td>
<td>2002</td>
<td>3.05 (1.80, 5.00)</td>
<td>1.04</td>
</tr>
<tr>
<td>Winter</td>
<td>2007</td>
<td>1.94 (1.14, 3.13)</td>
<td>18.30</td>
</tr>
<tr>
<td>Ip</td>
<td>2008</td>
<td>2.04 (1.68, 2.80)</td>
<td>1.07</td>
</tr>
<tr>
<td>Liu</td>
<td>2009</td>
<td>1.27 (0.75, 0.74)</td>
<td>1.07</td>
</tr>
<tr>
<td>Deng</td>
<td>2010</td>
<td>0.92 (0.64, 1.35)</td>
<td>17.22</td>
</tr>
<tr>
<td>Wu</td>
<td>2010</td>
<td>0.80 (0.36, 1.93)</td>
<td>0.41</td>
</tr>
<tr>
<td>Yingang</td>
<td>2010</td>
<td>1.02 (1.01, 1.03)</td>
<td>25.86</td>
</tr>
<tr>
<td>Ou</td>
<td>2013</td>
<td>1.08 (0.68, 1.75)</td>
<td>4.68</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.14 (0.86, 1.52)</td>
<td>105.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random-effects analyses.

Longitudinal Near Work
–Singapore (SCORM)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Risk</th>
<th>Cases</th>
<th>Controls</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Books Read per Week (Continuation Variable)</td>
<td>994</td>
<td>94</td>
<td>1.62 (1.08–2.40)</td>
<td>1.00 (0.62–1.61)</td>
</tr>
<tr>
<td>IQ, Number of Raven’s scores</td>
<td>440</td>
<td>168</td>
<td>1 (Reference)</td>
<td>1.00 (1.17–1.77)</td>
</tr>
<tr>
<td>Textile 1</td>
<td>250</td>
<td>136</td>
<td>1.50 (1.20–2.80)</td>
<td>1.50 (1.20–2.80)</td>
</tr>
<tr>
<td>Textile 2</td>
<td>368</td>
<td>190</td>
<td>1.00 (1.20–1.77)</td>
<td>1.00 (1.20–1.77)</td>
</tr>
</tbody>
</table>

Longitudinal Near Work
–Australia (SAVES)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Risk</th>
<th>Cases</th>
<th>Controls</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time outdoors</td>
<td>20.96</td>
<td>16.29</td>
<td>1.00 (0.57–1.77)</td>
<td></td>
</tr>
<tr>
<td>Outdoor leisure</td>
<td>16.27</td>
<td>14.09</td>
<td>1.00 (0.57–1.77)</td>
<td></td>
</tr>
<tr>
<td>Outdoor leisure</td>
<td>3.62</td>
<td>2.26</td>
<td>1.00 (0.57–1.77)</td>
<td></td>
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<tr>
<td>Near work</td>
<td>17.35</td>
<td>15.56</td>
<td>1.00 (0.57–1.77)</td>
<td></td>
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<tr>
<td>Near work</td>
<td>43.21</td>
<td>40.73</td>
<td>1.00 (0.57–1.77)</td>
<td></td>
</tr>
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</table>

Longitudinal Near Work
–United States (CLEERE)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Risk</th>
<th>Cases</th>
<th>Controls</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time outdoors</td>
<td>19.62</td>
<td>17.13</td>
<td>1.00 (0.57–1.77)</td>
<td></td>
</tr>
<tr>
<td>Outdoor leisure</td>
<td>15.85</td>
<td>13.66</td>
<td>1.00 (0.57–1.77)</td>
<td></td>
</tr>
<tr>
<td>Outdoor leisure</td>
<td>4.68</td>
<td>4.20</td>
<td>1.00 (0.57–1.77)</td>
<td></td>
</tr>
<tr>
<td>Near work</td>
<td>22.71</td>
<td>21.25</td>
<td>1.00 (0.57–1.77)</td>
<td></td>
</tr>
<tr>
<td>Near work</td>
<td>79.79</td>
<td>54.49</td>
<td>1.00 (0.57–1.77)</td>
<td></td>
</tr>
</tbody>
</table>

Longitudinal Near Work and Incidence, Score: 1/6

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Odds Ratio (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saw</td>
<td>2006</td>
<td>2</td>
<td>0.89 (0.97, 1.01)</td>
</tr>
<tr>
<td>Jones</td>
<td>2007</td>
<td>1.00 (0.96, 1.01)</td>
<td>79.88</td>
</tr>
<tr>
<td>Guggenheim</td>
<td>2012</td>
<td>1.22 (0.96, 1.58)</td>
<td>0.13</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.00 (0.96, 1.01)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Huang et al., PLoS One 2015
Near Work does not increase rate of progression

Time Outdoors Reduces Risk of Onset
Jones et al., Invest Ophthalmol Vis Sci, 2007

How much more time outdoors reduces risk of onset?
Xiong et al., Acta Ophthalmologica 2017

Time Outdoors and Risk of onset
- Saw et al. 2006 (SCORM): Time outdoors not associated with risk of onset
- Williams et al. 2008, Guggenheim et al. 2012 (ALSPAC): Time outdoors protective
- French et al. 2012 (SAVES): Time outdoors protective
- Zadnik et al. 2015 (CLEERE): Time outdoors protective
- Wu et al. (2013): Lower incidence rate in 1 year (8.41% vs. 17.65%)
- Wu et al. (2018): Lower incidence rate in 1 year (14.47% vs. 17.40%)
- He et al. 2015 (GOAL): Time outdoors protective (lower 3-year incidence 30.4% vs. 39.5%)

Time Outdoors does not slow rate of progression
More time outdoors no effect of progression

- Pärsinen & Lyra 1993: Time outdoors slower progression in boys
- Saw et. 2000 (SCORM): No effect
- Jones-Jordan et al. 2012 (CLEERE): No effect
- Wu et al. (2013): No effect
- Wu et al. (2018): Slower progression by 0.23 D
- He et al. 2015 (GOAL): Slower progression by 0.17 D over 3 years (but included the process of becoming myopic)

Time Outdoors and Rate of Progression

Growth in Axial Length—BIBS and OLSM

Decrease in Corneal Power—BIBS and OLSM

Decrease in Lens Power—BIBS and OLSM

Lens Thinning—BIBS and OLSM
Infancy—Emmetropization

Emmetropization—Time Course

- The eye registers the amount of hyperopia, then modifies the rate of axial growth to correct the refractive error
  - If more hyperopic, it grows faster
  - If less hyperopic or myopic, it grows slower
Local Control of Eye Growth

- form deprivation and hyperopic defocus (minus lenses) result in excess eye growth even if the optic nerve is cut
- excess eye growth only occurs for the sclera corresponding to the deprived visual field

Emmetropia

Hyperopic defocus from minus lenses

Myopic defocus from plus lenses
Compensation for Spectacle Lenses
Irving et al. (1992)

Emmetropization in the Monkey—
Smith and Hung (1999)

Does Initial Ref. Error Correlate with Refractive Change?

Emmetropization between 3 and 9 Months of Age—BIBS Data

- What visual signal explains emmetropization?
- Do infants behave like animals?
- What’s happening optically and structurally?

Defocus and Refractive Error
(unlike animal models)

Lag Uncorrelated with Ref. Change

R² = 0.006
P = 0.27
Acc. Effort Correlated with Ref. Change

\[ A_r = A_0 - \text{Acc. Error} = (U_{FP} - U_x) - \text{Acc. Error} \]

\[ R^2 = 0.17 \quad P < 0.0001 \]

**Emmetropization Theory**

- Emmetropization appears to be driven by visual feedback, but not as portrayed in animal models.
- May be more the response to accommodative effort than to accommodative lag.

**Who emmetropizes and why?**

**Does Early Correction of Hyperopia Affect Emmetropization?**

**Rx and Accommodative Training**
Can we Enhance Emmetropization?

Potential Impact of Hyperopia

Early Literacy

Test of Preschool Early Literacy (TOPEL)

VIP-HIP (Kulp et al., Ophthalmology, 2016)

Attributed to poor stereoacuity (poor near VA, poor sustained accommodation)

Potential Impact of Hyperopia

Distance Acuity

- For uncorrected children, those with acuity worse than 20/30*
  - plano to +2.00 D: 9%
  - +2.00 and more hyperopic: 31%

*Referral criterion from Pediatric Eye Evaluations
American Academy of Ophthalmology
Preferred Practice Pattern

Potential Impact of Hyperopia

Does impact on acuity depend on sign?
How much is too much?

Threshold Visual Acuity (LogMAR)

Accommodation Lag (D)

Age (Months)

TREATED
UNTREATED
CONTROLS

Does Early Correction of Hyperopia Affect Emmetropization?

Atkinson et al. (Eye, 1996)
**Relative Periph. Refraction**

- **Prolate**
- **Oblate**

<table>
<thead>
<tr>
<th>Visit Relative to Onset (years)</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.6</td>
<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

![Graph](image1.png)

**Accommodative Lag — 4D Badal**

- **Emmetrope Model**
- **Became Myopic**

<table>
<thead>
<tr>
<th>Visit Relative to Onset (years)</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.6</td>
<td>0.4</td>
<td>0.2</td>
<td>0.0</td>
<td>-0.2</td>
<td>-0.4</td>
</tr>
</tbody>
</table>

![Graph](image2.png)

**AC/A Ratio Increases**

- **Emmetrope Model**
- **Became Myopic**

<table>
<thead>
<tr>
<th>Visit Relative to Onset (years)</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
<td>0.8</td>
<td>0.6</td>
<td>0.4</td>
<td>0.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

![Graph](image3.png)

**Axial Length**

- **Emmetrope Model**
- **Became Myopic**

<table>
<thead>
<tr>
<th>Visit Relative to Onset (years)</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22.5</td>
<td>23.0</td>
<td>23.5</td>
<td>24.0</td>
<td>24.5</td>
<td>25.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph](image4.png)

**Ciliary Muscle Imaging**

*Bailey et al. (2008)*

![Image](iris_photo.png)


Iris photo: Jan Drewes
Ciliary Muscle in Myopia

Bailey et al. (2008)

![Graph showing Ciliary Body Thickness vs. Cycloplegic Refractive Error (D)]

What’s so good about time outdoors?

- Better image quality
  - peripheral optics (Flitcroft, 2013)
  - pupil size
- Physical activity
- UVB and vitamin D
- Bright visible light and dopamine release

Actions of Vitamin D

Regulation of eye growth?

- Both 1,25(OH)2D3 and RA regulate cell differentiation, proliferation, and apoptosis (Tavera-Mendoza, 2006)
- Vitamin D receptor interacts with retinoic acid receptors and retinoid X receptors
- Dietary RA increases eye length in chick (McFadden et al., 2006)
- RAR mRNA expression upregulated with FD myopia (Morgan et al., 2004)

Vitamin D in the News

Vitamin D has a long list of benefits

By David Templeton

*Pittsburgh Post-Gazette*

Wednesday, June 03, 2009

“Lack of vitamin D is a major factor in the pathology of at least 17 varieties of cancers including breast and prostate cancers, heart disease, stroke, hypertension, autoimmune disease, diabetes, depression, chronic pain, osteoarthritis, osteoporosis, muscle weakness, muscle wasting, birth defects and periodontal disease…”

...add multiple sclerosis

Vitamin D Nutritional Levels

- Average levels 24 ng/ml (60 nM; Chapuy et al., *Osteoporos Int*, 1997)

<table>
<thead>
<tr>
<th>ng/mL</th>
<th>nmol/L</th>
<th>Health status</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11</td>
<td>&lt;27.5</td>
<td>Deficient</td>
</tr>
<tr>
<td>&lt;10 - .15</td>
<td>&lt;25 - 37.5</td>
<td>Inadequate</td>
</tr>
<tr>
<td>15 - 30</td>
<td>37.5 - 75</td>
<td>Adequate</td>
</tr>
<tr>
<td>≥30</td>
<td>≥75</td>
<td>Desirable</td>
</tr>
<tr>
<td>Consistently &gt;200</td>
<td>Consistently &gt;500</td>
<td>Toxic</td>
</tr>
</tbody>
</table>

Adapted from: http://ods.od.nih.gov/factsheets/vitamin-d.asp#h3
Dietary Intake and Sun Exposure
- The consumption of 1 μg (40 IU/day) of vitamin D3 raises serum 25(OH)D by 1 nM (0.4 ng/ml).


Phase Delay in Vitamin D levels
- Pittaway et al., *PLoS One*, 2013

Lower Blood Vitamin D in Myopes
- Mutti and Marks, *Optom Vis Sci*, 2011

<table>
<thead>
<tr>
<th>Factor</th>
<th>Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food folate (per μg/day)</td>
<td>-0.035</td>
<td>0.001</td>
</tr>
<tr>
<td>Sugars—Total (per g/day)</td>
<td>-0.012</td>
<td>0.001</td>
</tr>
<tr>
<td>Calcium (per mg/day)</td>
<td>0.010</td>
<td>0.006</td>
</tr>
<tr>
<td>Theobromine (per mg/day)</td>
<td>0.10</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Demographic
- Age (per year)        | 0.32        | 0.026   |
- Myopic (ng/ml lower)  | -3.4        | 0.005   |

VDR SNP Variations

VDR Multivariate Results

<table>
<thead>
<tr>
<th>SNP</th>
<th>Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2239182 (G)</td>
<td>2.17</td>
<td>0.007</td>
</tr>
<tr>
<td>rs3819545 (C)</td>
<td>2.34</td>
<td>0.003</td>
</tr>
<tr>
<td>rs2853559 (T)</td>
<td>2.14</td>
<td>0.0035</td>
</tr>
<tr>
<td>rs7041 (G)</td>
<td>1.64</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Other Myopia GWAS Results
- OR = 1.16 for rs8027411 in *RASGRF1* (Ras protein-specific guanine nucleotide-releasing factor 1) at 15q25 (Hysi et al., 2010)
- OR = 1.83 for rs634990 near *GJD2* (Connexin36) and *ACTC1* (SMA cardiac muscle alpha actin 1) at 15q14 (Solouki et al., 2010)
- R² = 0.5%
- Over 40 loci now associated (R² = 2.9-3.4%) (Verhoeven et al., 2013; Kiefer et al., 2013)
Vitamin D and Korean Adolescents

Choi et al., Invest Ophthalmol Vis Sci, 2014

- 2,038 adolescent aged 13–18 years, who participated in the Korea National Health and Nutrition Examination Survey (KNHANES) from 2008 to 2011
- 80.1% had myopia (-0.5 D or more myopic)
- 0.03ng/ml lower per diopter of myopia ($R^2 = 0.45\%$), adjusted for age, sex, income, diet, smoking

Odds Ratios for High Myopia

Choi et al., Invest Ophthalmol Vis Sci, 2014

<table>
<thead>
<tr>
<th>Serum vitamin D group</th>
<th>Odds ratio for High Myopia (-6.00 D; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18.4 compared to &lt;13.8 male</td>
<td>0.55 (0.34, 0.90)</td>
</tr>
<tr>
<td>≥17.0 compared to &lt;13.0 female</td>
<td>0.69 (0.41, 1.14)</td>
</tr>
<tr>
<td>&lt;18.4 compared to &lt;13.8 male</td>
<td>0.55 (0.34, 0.90)</td>
</tr>
<tr>
<td>&lt;17.0 compared to &lt;13.0 female</td>
<td>0.69 (0.41, 1.14)</td>
</tr>
</tbody>
</table>

- No data on total time outdoors, parental myopia, season of measurement, and sunlight exposure
- Recently repeated in Western Australian Pregnancy Cohort (Raine) Study (Yazar et al., IOVS 2014)

What's Good about Time Outdoors?

- Visible Light and Retinal Dopamine
  - Sunlight stimulates dopamine release from retinal neurons (Witkovsky P., Doc Ophthalmol. 2004)
  - Chicks raised in elevated light levels showed 30% higher retinal DOPAC levels compared to standard light (Norton T. T. et al., Exp Eye Res. 2013)
  - Inhibits form deprivation in rhesus monkeys (Smith III E.L., Hung L. and Huang J., IOVS. 2012)
Compensation for Spectacle Lenses
Irving et al. (1992)

Illumination and Experimental Myopia
Ashby et al. (2009, 2010)

Illumination and Experimental Myopia
Smith et al. (2011, 2013)

Time Outdoors Interventions

Visible Light and Retinal Dopamine

• ipRGCs
  – Photoreceptor in ganglion cell layer
  – Melanopsin photopigment
  – Photon counters
    • Project to suprachiasmatic nucleus
    • Entrain circadian rhythms
  – Synapse with sustained light response dopaminergic amacrine cells (Zhang et al., PNAS 2008)
  – Project to olivary pretectal nucleus, pupil response (Gamlin et al., Exp Brain Res 1995)

from Zhang et al., PNAS 2008

Protection abolished by D. receptor antagonist spiperone
Pupillary Assessment

- RAPDx pupillometer (Konan Medical)
- Blue light (peak at 448 nm), presumed stimulation of ipRGCs (Park J. C. et al. IOVS. 2011)
- Red light (peak at 608 nm), preferential stimulation of long-wavelength cone photoreceptors
- Testing sequence
  - 5 min. dark adaptation before each sequence
  - 1. Alternating red and blue
  - 2. Red only
  - 3. Blue only
  - All

Red
Blue

0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

Time (sec)

Blue Red

Myopes
Non-Myopes

n = 28
n = 16

Results – Children
Red vs. Blue

ΔBlue
SEQ Refractive Error (D)

r = 0.48
p = 0.001

Non-Myopic Single Color
Myopic Single Color

Normalized Pupil Size

Time (sec)

Normalized Pupil Size

Time (sec)
**Hypothesized Mechanism**

- Adaptive response to repeated light exposure consistent with the hypothesis that dopamine is modifying retinal networks
  - Both ipRGC- and photoreceptor-driven
    (Hayashida et al., *J Neurosci* 2009 and Vaquero et al., *J Neurosci* 2001)

- Adaptive mechanisms in children may be a pathway through which time outdoors influences retinal dopamine release, axial elongation, and ultimately refractive error development

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**Why an Effect on Risk of Onset but not Rate of Progression?**

- Limited amount of time spent outdoors by myopes?
- Onset and progression represent two different processes?
- Myopes have a deficiency in registering the amount and effects of time outdoors?
  - ...and spend less time outdoors
**Time Outdoors and Light Exposure**

- Subjects wore illuminance monitoring badges that recorded light exposure every minute (Daysimeter).
- Subjects wore badges outside their clothes for 6.9 ± 0.3 days during waking hours.
- Data analyzed at 1, 3, 12 hours and 1, 3, 5 days.
- Log lux-minute values.

**Conclusions**

- The prevalence of myopia is increasing in Asia but not so much in the US (between 25-33% for decades).
- Myopia is strongly genetic, but...
- Near work is not an important environmental factor.
- Time outdoors is an important environmental factor.
- Children are spending more time indoors, children read indoors, but being indoors seems more relevant to myopia than what a child does indoors.

**Refractive error by light exposure interaction**

- Slower redilation: More ipRGC input.
- Faster redilation: Less ipRGC input.

**Non-Myopes**

- Slower redilation: More ipRGC input.
- Faster redilation: Less ipRGC input.

**Low Myopes**

- Slower redilation: More ipRGC input.
- Faster redilation: Less ipRGC input.

**Moderate Myopes**

- Slower redilation: More ipRGC input.
- Faster redilation: Less ipRGC input.

**Conclusions**

- Time outdoors reduces the risk of the onset of myopia but not the rate of progression.
- Bright light schools are having that effect.
- Time outdoors seems to be more about bright visible light and retinal dopamine release than UVB and vitamin D or exercise.
- Retinal cells connected to dopamine release and circadian rhythm (ipRGCs) evaluated by pupil responses seem different between myopes and non-myopes.
Conclusions

• Some myopes seem to have reduced ability to benefit from time outdoors in addition to spending less time outdoors.

• Born that way or is this from time outdoor habits? Can it be changed?

• Are certain parts of the spectrum more important than others and why?

• Intense UV and short wavelength exposures are harmful. Is there another way to get the same benefit?

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