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Environmental Influences on Myopia

Donald O. Mutti, OD, PhD, FAAO

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Financial Disclosures

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

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The CLEERE Study Group

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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.

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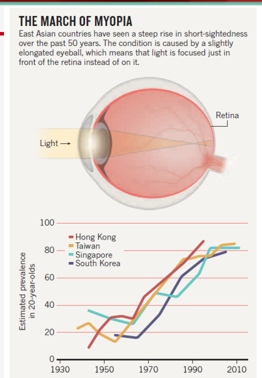
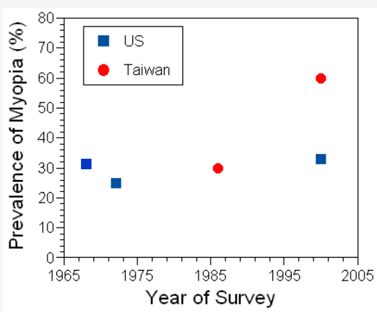


Dolgin
The Myopia Boom
Nature, 2015

E. Dolgin,
Nature: News & Comment
2015

Increase in Prevalence with Time?



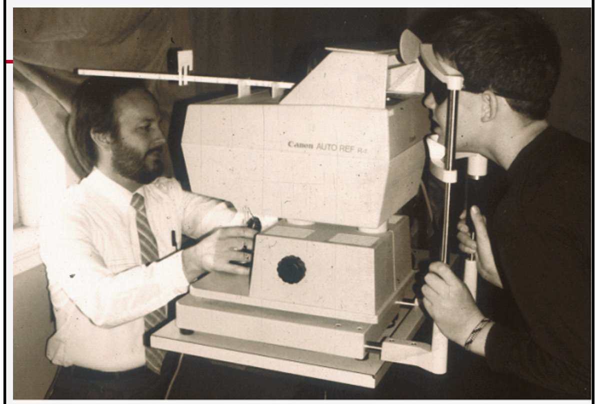
Orinda Longitudinal Study of Myopia

- 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

Orinda Longitudinal Study of Myopia

- cycloplegic autorefraction (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



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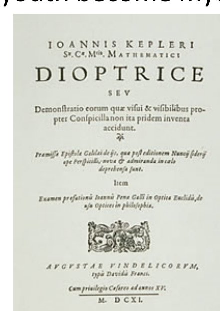
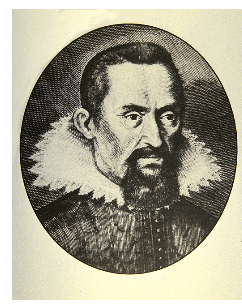
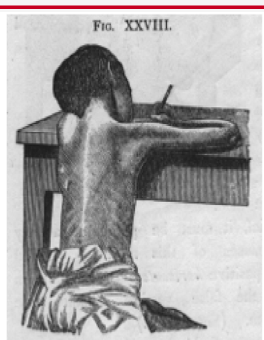
“Those who do much close work in their youth become myopic.”


IOANNIS KEPLERI
S.C.M. MATHEMATICI
DIOPTRICE
SEV
Demonstratio eorum quæ visui & visibilibus propter Conspicilla non ita pridem inventa accidunt.
AVGVSTAE VINDELICORVM,
M. DCXI.



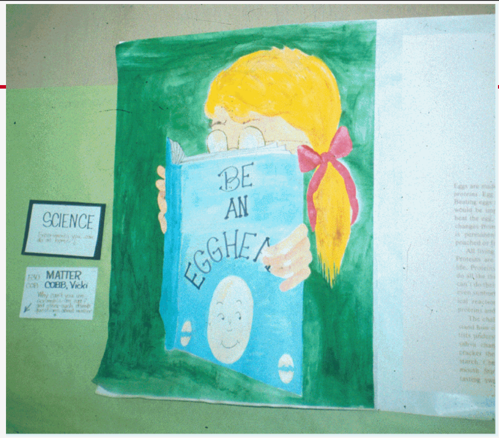
Near Work—Cohn (1886)
The Hygiene of the Eye in Schools



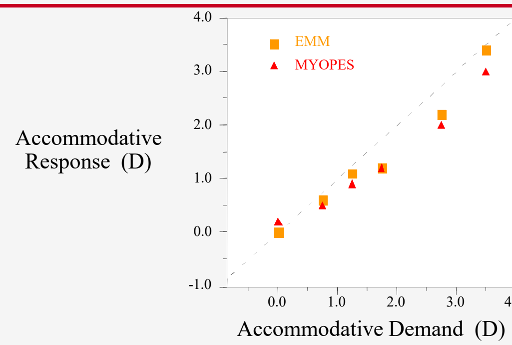
- 1% of 240 village schoolchildren were myopic
- 13% to 60% of 361 city schoolchildren were myopic

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

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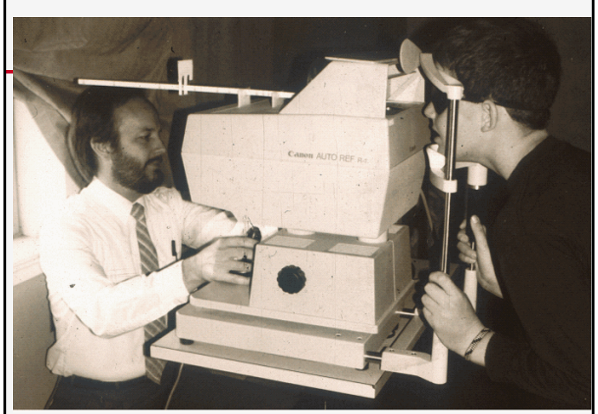
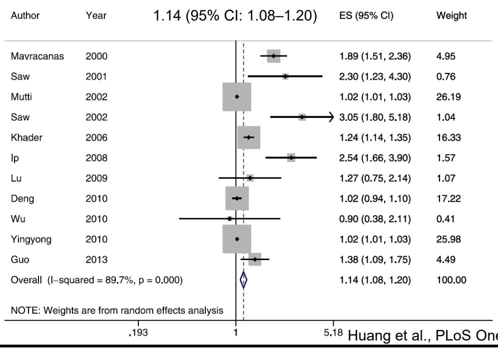
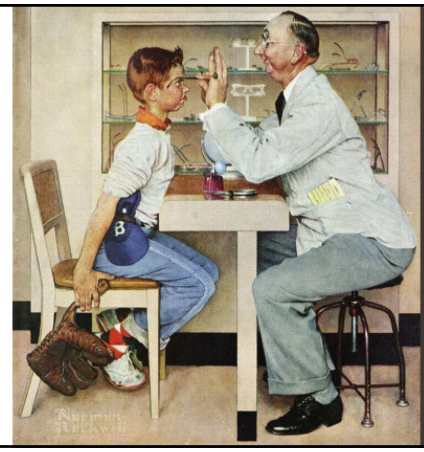
- became CLEERE: 4,929 children across US for ethnic diversity by 2010



Cross-sectional Near Work and Prevalence, Score: 10/15



Huang et al., PLoS One 2015



Longitudinal Near Work
–Singapore (SCORM)

Saw et al. (2006)

	At Risk (*n*)	Cases (*n*)	Crude RR Myopia at least −0.75 D (95% CI)	Age, Sex, Income RR Myopia at least −0.75 D (95% CI)	Multivariable RR* Myopia at least −0.75 D (95% CI)
Books Read per Week (Continuous Variable)	994	454	1.02 (0.98–1.06)	1.00 (0.92–1.10)	1.01 (0.97–1.05)
IQ, tertiles of Raven score†					
Tertile 1	440	168	1 (Referent)	1 (Referent)	1 (Referent)
Tertile 2	256	130	1.40 (1.12–1.75)	1.39 (1.11–1.76)	1.37 (1.08–1.72)
Tertile 3	298	156	1.50 (1.20–1.88)	1.51 (1.20–1.90)	1.50 (1.19–1.89)

"…number of hours of reading per day (RR 0.99; 95% CI, 0.92–1.07)
computer use (RR 0.94; 95% CI, 0.77–1.15)
number of hours playing video games per day (RR 0.94; 95% CI, 0.80 –1.09)
number of hours watching television per day (RR 0.96; 95% CI, 0.87–1.06)
diopter-hours (RR 0.99; 95% CI, 0.97–1.01)
total number of near work hours per day (RR 0.97; 95% CI, 0.93–1.01)…
…were not associated with incident myopia in multivariate analyses."

Longitudinal Near Work, Time Outdoors
–Australia (SAVES)

French et al. (2013)

Activities	Younger Cohort: Remained Nonmyopic (Mean/Week)	Younger Cohort: Incident Myopia (Mean/Week)	*P* Value
Time outdoors (hr)	20.96	16.29	<0.0001
Outdoor leisure (hr)	18.27	14.08	<0.0001
Outdoor sport (hr)	3.60	2.76	0.049
Near work (hr)	17.55	19.36	0.020
Near work (D-hr)	43.21	49.73	0.022

Activities	Older Cohort: Remained Nonmyopic (Mean/Week)	Older Cohort: Incident Myopia (Mean/Week)	*P* Value
Time outdoors (hr)	19.62	17.15	0.001
Outdoor leisure (hr)	15.85	13.66	0.001
Outdoor sport (hr)	4.69	4.28	0.27
Near work (hr)	20.71	22.08	0.062
Near work (D-hr)	79.79	84.49	0.11

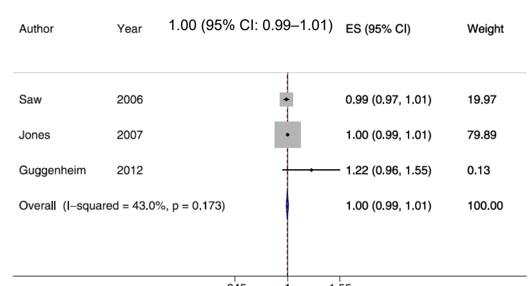
Longitudinal Near Work, Time Outdoors
–United States (CLEERE)

Zadnik et al. (2015)

Table 2. Univariate Analysis of Risk Factors for Developing Myopia

Variable	Odds Ratio (95% CI)[a]: Grade 1	Grade 3	Grade 6
No. of myopic parents			
1	1.35 (1.03-1.76)[d]	1.36 (1.05-1.76)[d]	1.77 (1.19-2.62)[c]
2	2.23 (1.63-3.04)[b]	2.40 (1.76-3.27)[b]	3.51 (2.18-5.64)[b]
Visual activity, diopter-hour	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Time spent outdoors, h/wk	0.98 (0.97-1.00)[d]	0.97 (0.95-0.98)[b]	0.96 (0.94-0.99)[d]

Longitudinal Near Work and Incidence, Score: 1/6



Huang et al., PLoS One 2015

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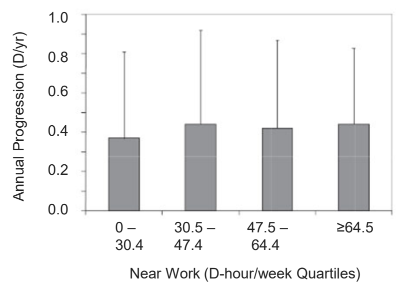
Near Work does not increase rate of progression

Jones-Jordan et al., *Invest Ophthalmol Vis Sci, 2012*



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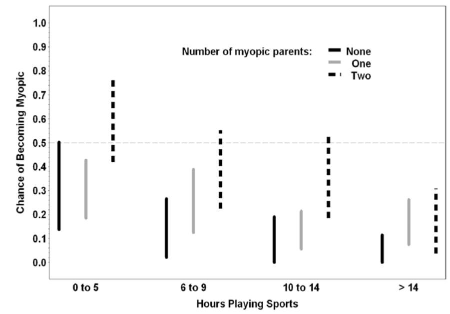
Time Outdoors Reduces Risk of Onset

Jones et al., *Invest Ophthalmol Vis Sci,* 2007



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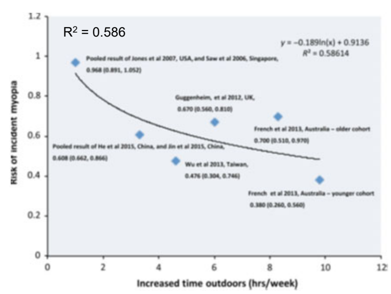
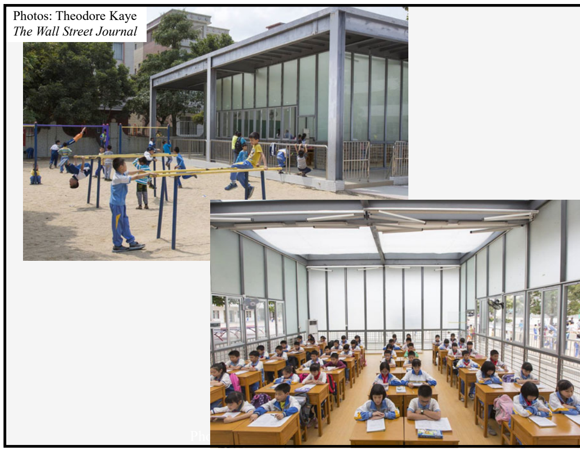
How much more time outdoors reduces risk of onset?



Xiong et al., *Acta Ophthalmologica* 2017

Photos: Theodore Kaye
The Wall Street Journal



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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%)

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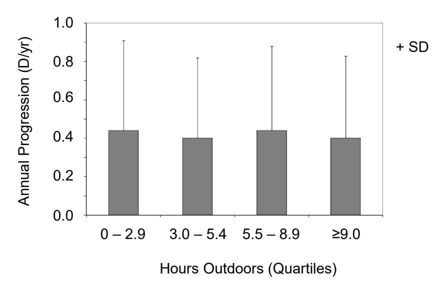
Time Outdoors does not slow rate of progression

Jones-Jordan et al., *Invest Ophthalmol Vis Sci, 2012*



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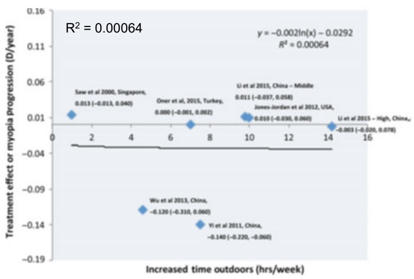
More time outdoors no effect of progression



Xiong et al., *Acta Ophthalmologica* 2017

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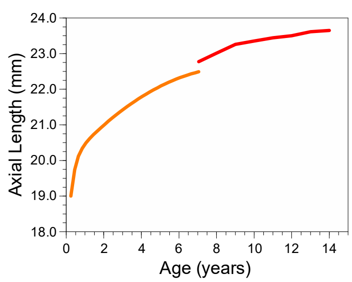
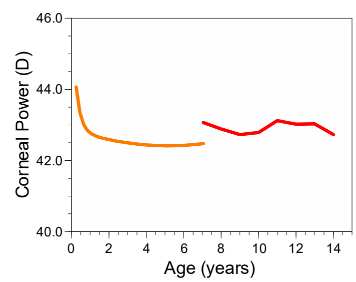
Time Outdoors and Rate of Progression

- Pärssinen & Lyyra 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)

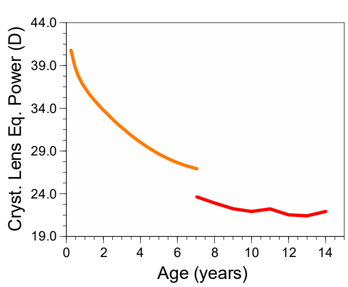
Growth in Axial Length—
BIBS and OLSM



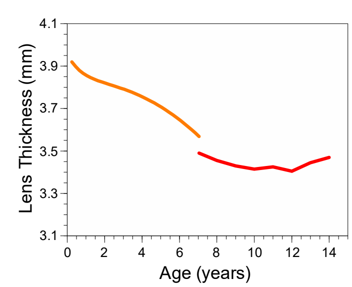
Decrease in Corneal Power—
BIBS and OLSM

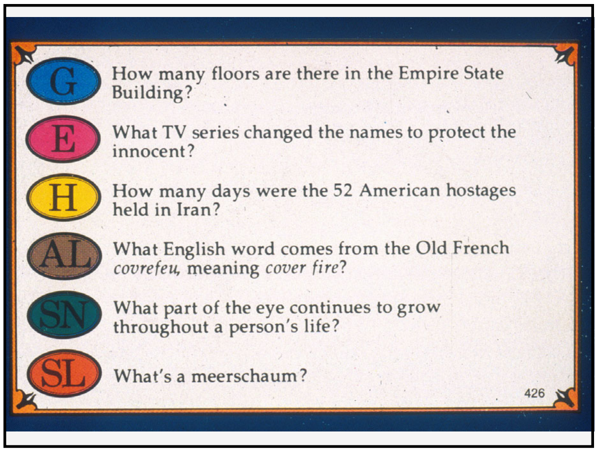


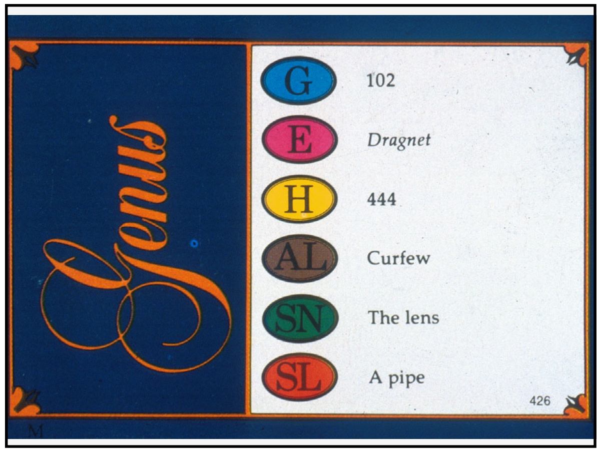
Decrease in Lens Power—
BIBS and OLSM



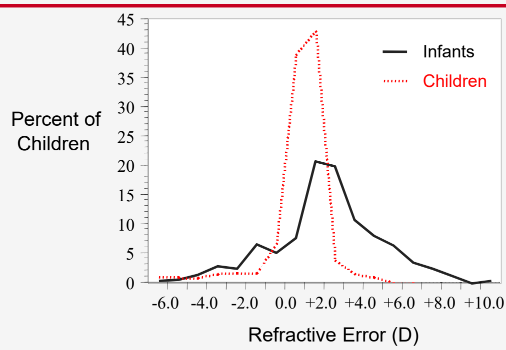
Lens Thinning—
BIBS and OLSM

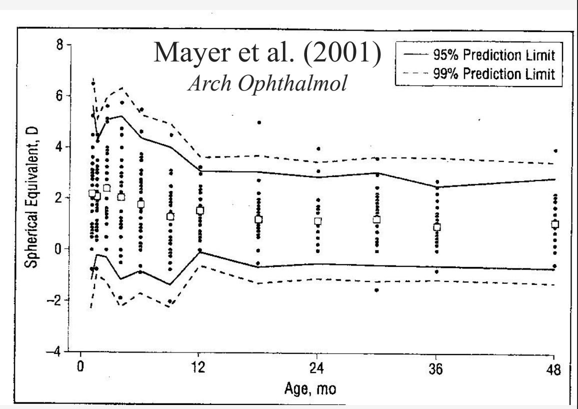




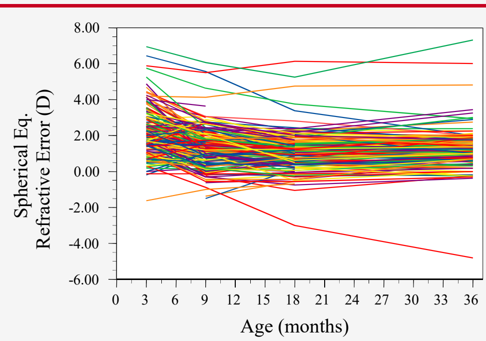


Infancy—Emmetropization





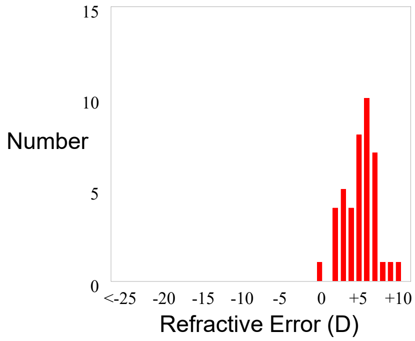
Emmetropization—Time Course



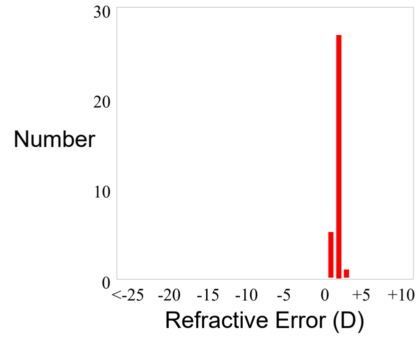
Emmetropization Mechanism–Active Visual Feedback

- 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

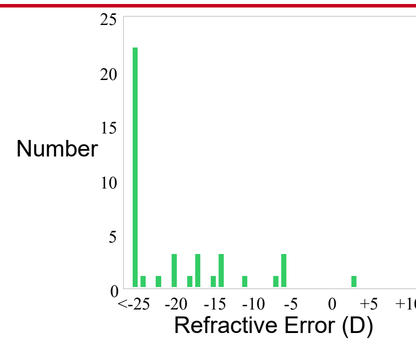
Normal Chick at 2 Weeks
Wallman et al. (1981)



Normal Chick at 8 Weeks
Wallman et al. (1981)

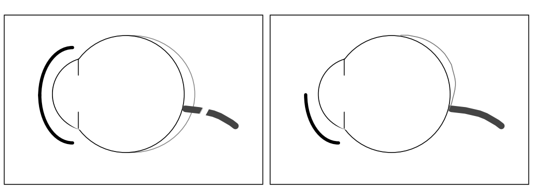


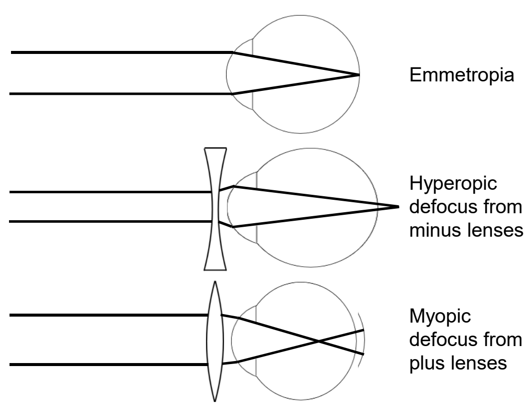
After 2 Weeks of Form Deprivation
Wallman and Adams (1987)



Local Control of Eye Growth

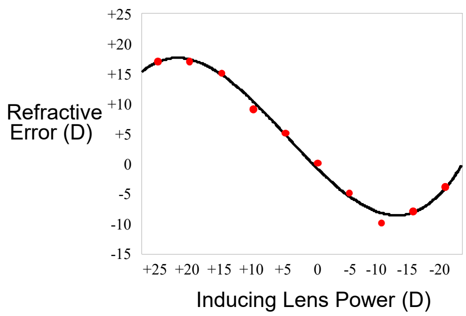
- form deprivation and hyperopic defocus (minus lenses) result in excess eye growth even if the optic nerve is cut
- excess eye growth only occurs for the sclera corresponding to the deprived visual field





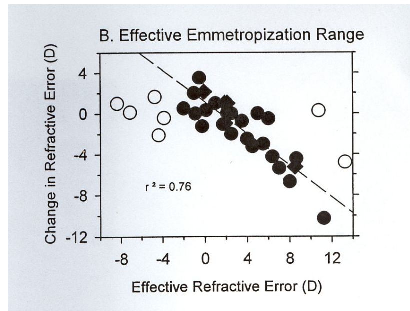
Compensation for Spectacle Lenses

Irving et al. (1992)

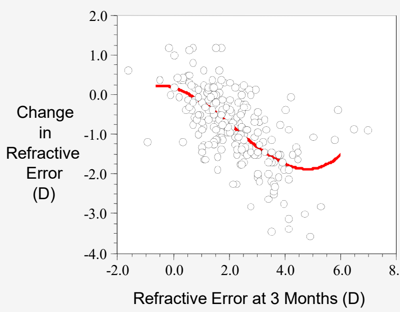


Emmetropization in the Monkey—

Smith and Hung (1999)



Does Initial Ref. Error Correlate with Refractive Change?



$R^2 = 0.41$

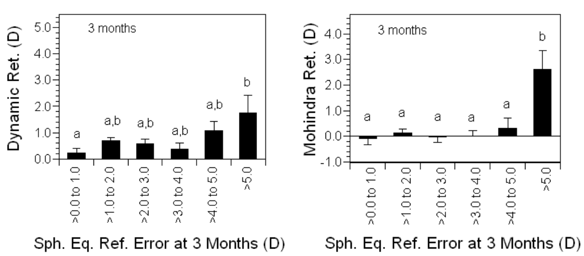
P < 0.0001

Emmetropization between 3 and 9 Months of Age—BIBS Data

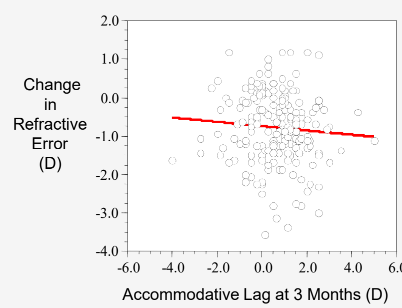
- What visual signal explains emmetropization?
- Do infants behave like animals?
- What's happening optically and structurally?

Defocus and Refractive Error

(unlike animal models)



Lag Uncorrelated with Ref. Change

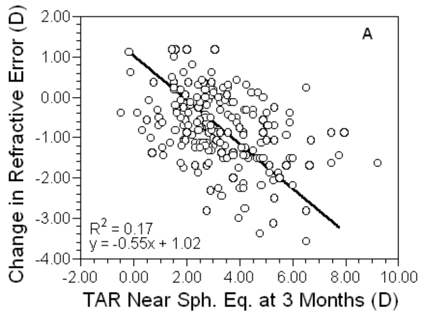


$R^2 = 0.006$

P = 0.27

Acc. Effort Correlated with Ref. Change

$A_r = A_o - \text{Acc. Error} = (U_{FP} - U_x) - \text{Acc. Error}$

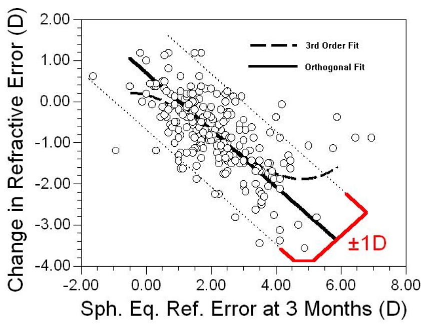


$R^2 = 0.17$
$P < 0.0001$

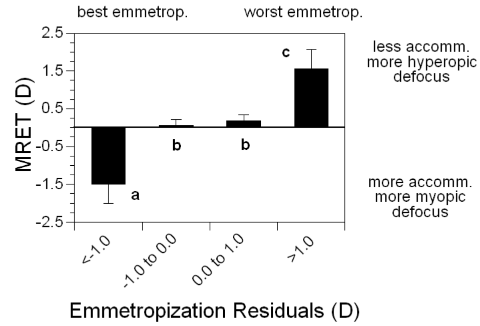
Emmetropization Theory

- 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?

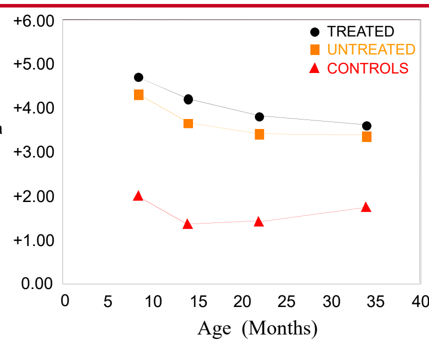


Who emmetropizes and why?



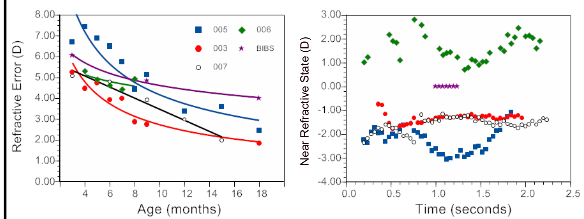
Does Early Correction of Hyperopia Affect Emmetropization?

Atkinson et al. (*Eye*, 1996)



Rx and Accommodative Training

Can we Enhance Emmetropization?



Potential Impact of Hyperopia
Early Literacy

Table 3. Test of Preschool Early Literacy Scores by Refractive Error Group

TOPEL Score	Emmetropic (n = 248) Mean	SD	Hyperopic (3–6 D) (n = 244) Mean	SD	Unadjusted Difference (95% CI)	P	Adjusted* Difference (95% CI)	P
Total	89.4	23.5	83.5	22.9	−5.9 (−10.0 to −1.8)	0.004	−4.3 (−7.7 to −0.9)	0.01
Print Knowledge	22.9	10.7	19.7	11.3	−3.1 (−5.1 to −1.2)	0.002	−2.4 (−4.1 to −0.6)	0.007
Definitional Vocabulary	51.2	11.2	48.9	11.1	−2.3 (−4.3 to −0.3)	0.02	−1.6 (−3.4 to 0.3)	0.07
Phonological Awareness	15.4	5.4	14.9	4.8	−0.5 (−1.4 to 0.4)	0.28	−0.3 (−1.1 to 0.4)	0.39

CI = confidence interval; SD = standard deviation; TOPEL = Test of Preschool Early Literacy.
*Adjusted for age at testing in months, race, and ethnicity of participant, and education level of parent or caregiver.

Test of Preschool Early Literacy (TOPEL)

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

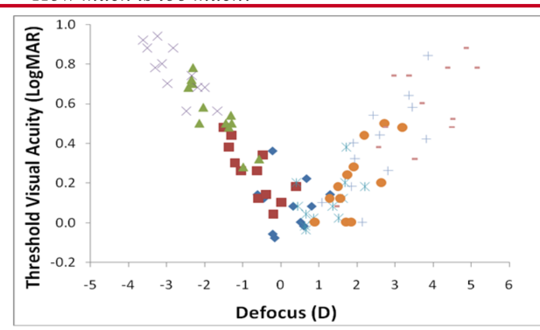
Attributed to poor stereoacuity (poor near VA, poor sustained accommodation)

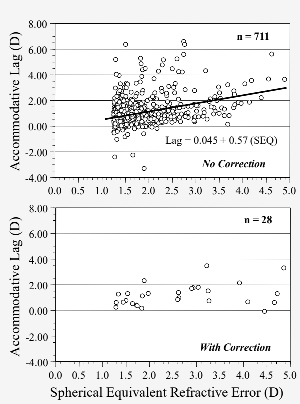
Potential Impact of Hyperopia
Distance Acuity

- 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

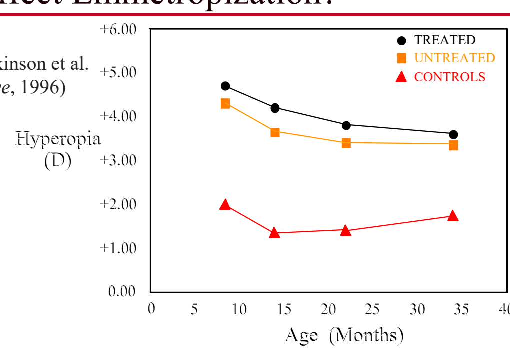
Potential Impact of Hyperopia
Does impact on acuity depend on sign?
How much is too much?



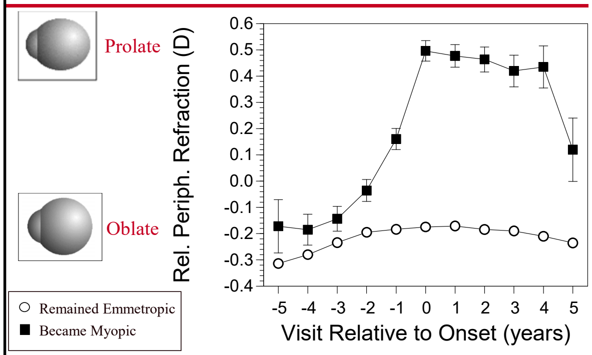


Does Early Correction of Hyperopia Affect Emmetropization?

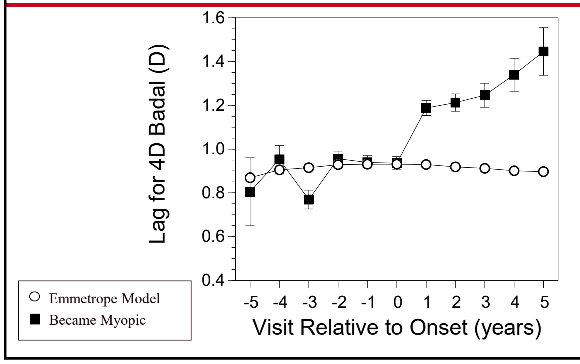
Atkinson et al. (*Eye*, 1996)



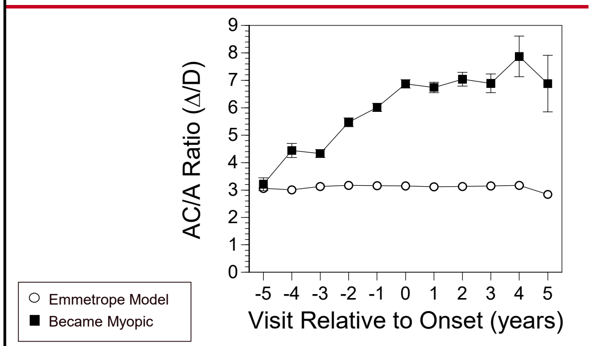
Relative Periph. Refraction



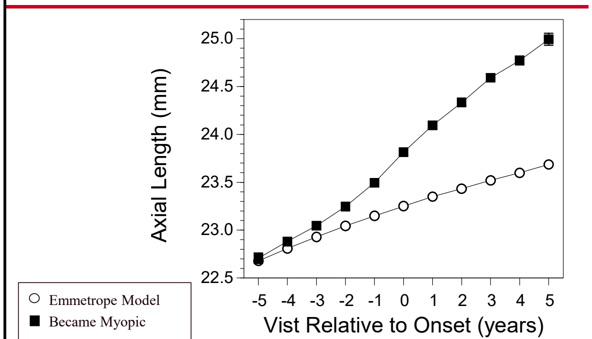
Accommodative Lag — 4D Badal

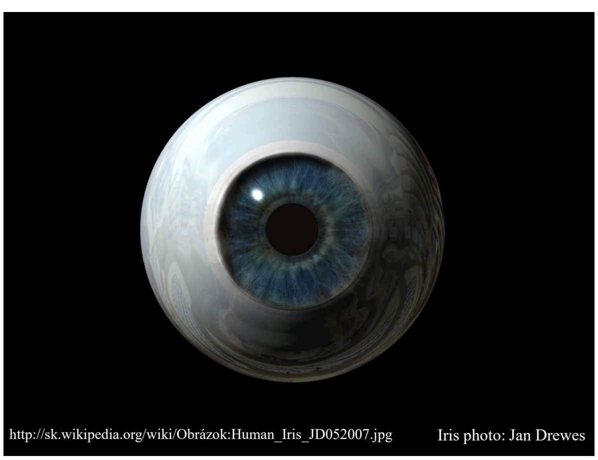


AC/A Ratio Increases



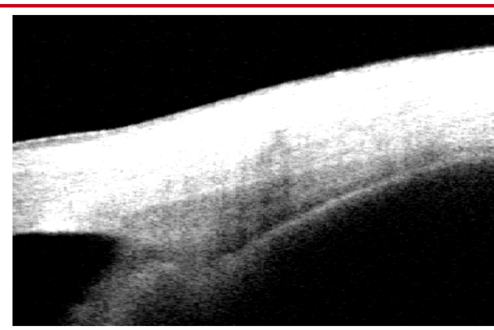
Axial Length





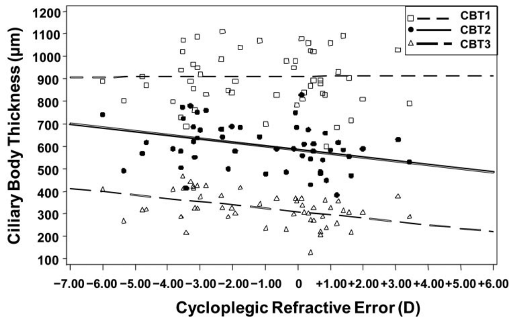
Ciliary Muscle Imaging

Bailey et al. (2008)



Ciliary Muscle in Myopia

Bailey et al. (2008)



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 $1,25(OH)_2D_3$ 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

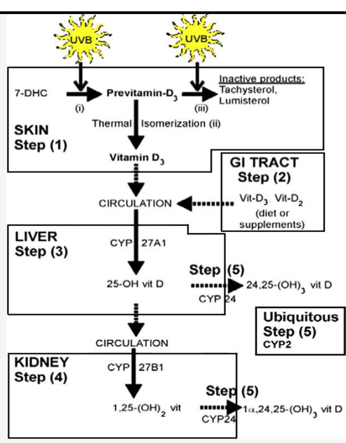
By David Templeton

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 photosynthesis

Wolpowitz and Gilchrest

J Am Acad Dermatol, 2006

Vitamin D Nutritional Levels

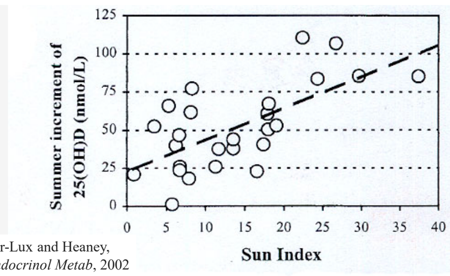
- Average levels 24 ng/ml (60 nM; Chapuy et al., *Osteoporos Int*, 1997)

ng/mL	nmol/L	Health status
<11	<27.5	Deficient
<10 -15	<25 - 37.5	Inadequate
15 -30	37.5 - 75	Adequate
≥30	≥75	Desirable
Consistently >200	Consistently >500	Toxic

Adapted from: http://ods.od.nih.gov/factsheets/vitamind.asp#h3

Dietary Intake and Sun Exposure

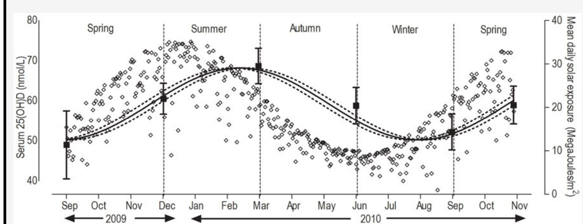
- The consumption of 1 µg (40 IU/day) of vitamin D_3 raises serum 25(OH)D by 1 nM (0.4 ng/ml)



Barger-Lux and Heaney, *J Clin Endocrinol Metab*, 2002

Phase Delay in Vitamin D levels

Pittaway et al., PLoS One, 2013



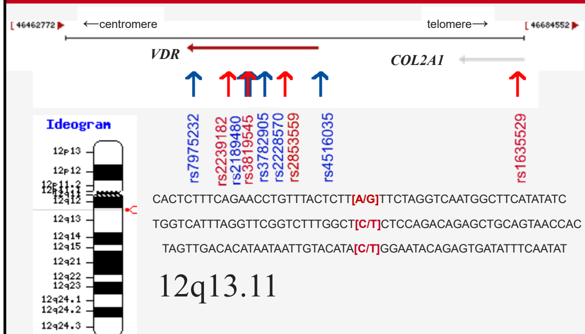
n = 91 60–85 year old community-dwelling adults in Tasmania

Lower Blood Vitamin D in Myopes

Mutti and Marks, Optom Vis Sci, 2011

Factor	Coefficient	p-value
Diet		
Food folate (per µg/day)	-0.035	0.001
Sugars—Total (per g/day)	-0.012	0.001
Calcium (per mg/day)	0.010	0.006
Theobromine (per mg/day)	0.10	<0.0001
Demographic		
Age (per year)	0.32	0.026
Case Status		
Myopic (ng/ml lower)	-3.4	0.005

VDR SNP Variations



VDR Multivariate Results

Mutti et al., Invest Ophthalmol Vis Sci, 2011

- Whites only
- Myopic (−0.75 D to −4.00 D): n = 141
- Control (≥+0.50 D): n = 73

$R^2 = 18.0\%$

SNP	Odds Ratio	p-value
rs2239182 (G)	2.17	0.007
rs3819545 (C)	2.34	0.003
rs2853559 (T)	2.14	0.0035
rs7041 (G)	1.64	0.030

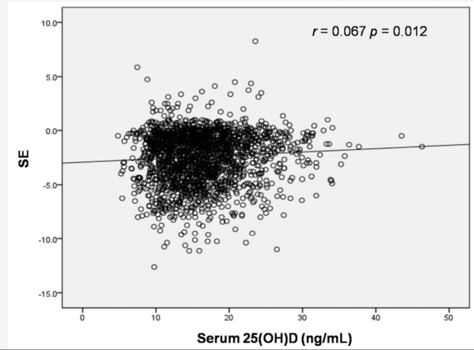
Other Myopia GWAS Results

- 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)
- $R^2 = 0.5\%$
- Over 40 loci now associated ($R^2 = 2.9\text{-}3.4\%$) (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

Association between SEQ and Vitamin D
Choi et al., Invest Ophthalmol Vis Sci, 2014



Odds Ratios for High Myopia
Choi et al., Invest Ophthalmol Vis Sci, 2014

Serum vitamin D group	Odds ratio for High Myopia (-6.00 D; 95% CI)
≥18.4 compared to <13.8 male ≥17.0 compared to <13.0 female	0.55 (0.34, 0.90)
<18.4 compared to <13.8 male <17.0 compared to <13.0 female	0.69 (0.41, 1.14)

- 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)

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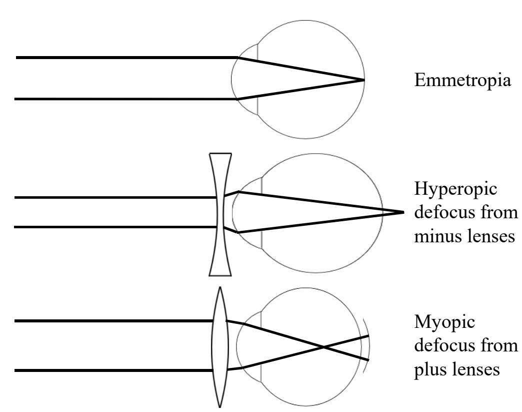
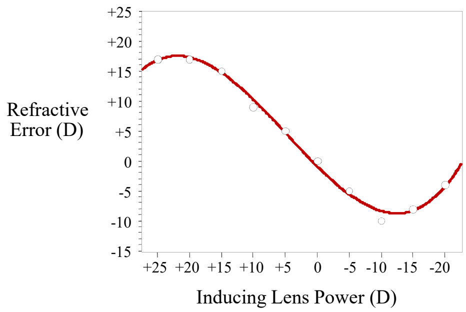
What's Good about Time Outdoors?

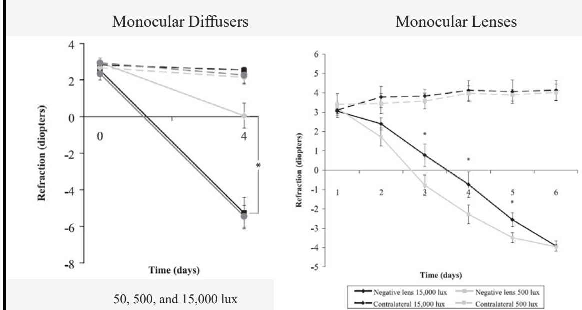
- Visible Light and Retinal Dopamine
  - Sunlight stimulates dopamine release from retinal neurons (Witkovsky P., *Doc Ophthalmol*. 2004)
  - Chicks raised in elevated light levels showed 30% higher retinal DOPAC levels compared to standard light (Norton T. T. et al., Exp Eye Res. 2013)
  - Inhibits ocular growth in chick models (Feldkaemper M. and Schaeffel F., *Exp Eye Res*. 2013; Ashby R. S. and Schaeffel F., *Invest Ophthalmol Vis Sci*. 2010)
  - 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)

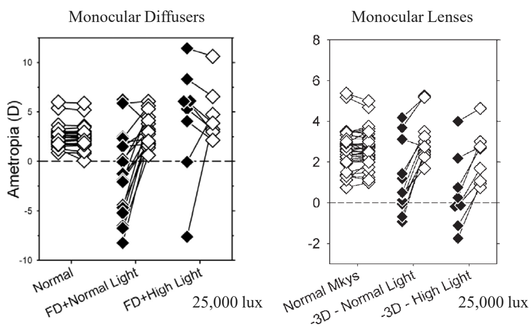


Illumination and Experimental Myopia
Ashby et al. (2009, 2010)



Protection abolished by D_2 receptor antagonist spiperone

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



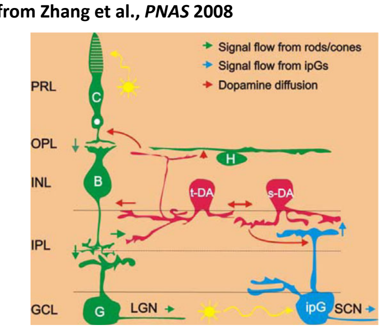
Time Outdoors Interventions

- 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%)

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



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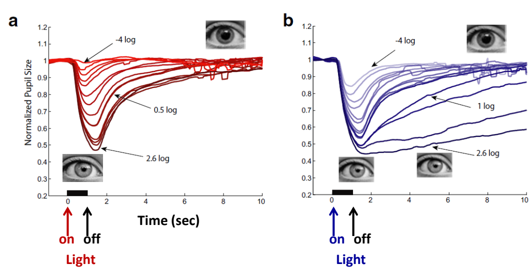
from Park et al., *IOVS* 2011



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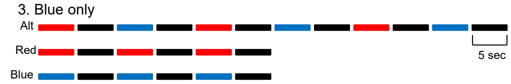
Pupillary Assessment

- 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



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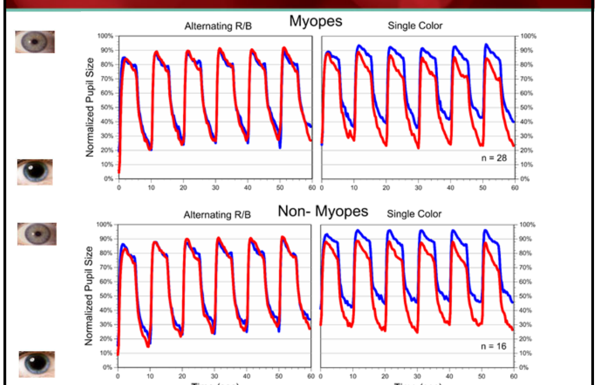

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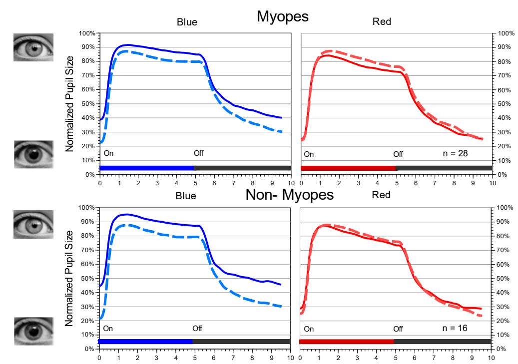

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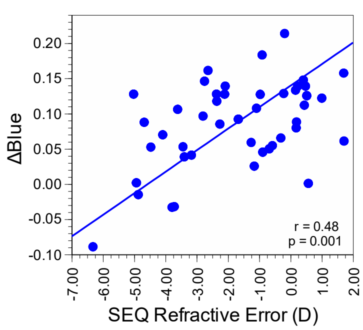

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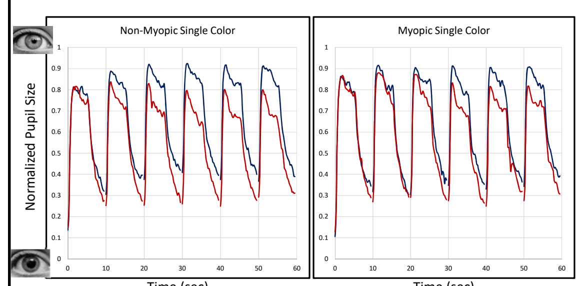
Results – Children Red vs. Blue



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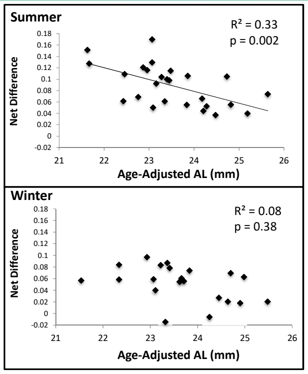

Children By Season

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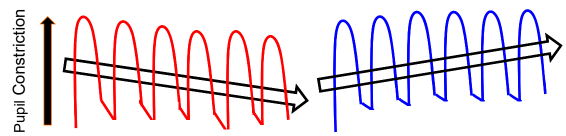
Hypothesized Mechanism

- This rise in dopamine inhibits cone-driven paths
  - Vaquero et al. 2001; Hayashida et al. 2009

  … and potentiates melanopsin-driven paths
  - Van Hook et al., 2012; Sodhi & Hartwick, 2014
- Results in decreased pupil constriction during red-only test and increased during blue-only test



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Hypothesized Mechanism

- Adaptive response to repeated light exposure consistent with 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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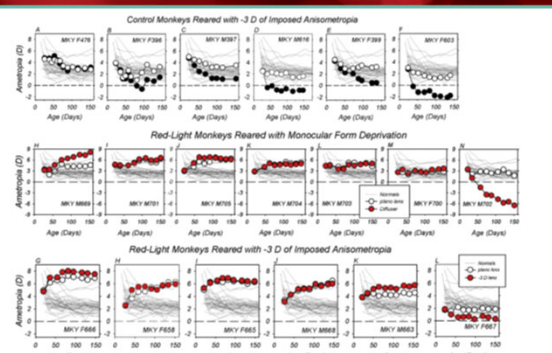

Hung et al., *Exp Eye Research* 2018

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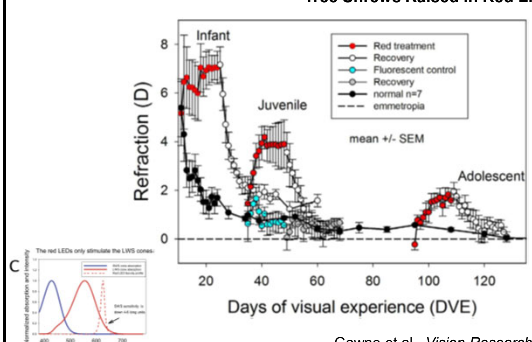
Tree Shrews Raised in Red Light



Gawne et al., *Vision Research* 2017

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

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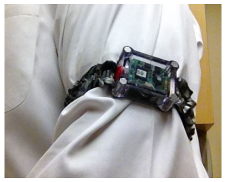
Time Outdoors and Light Exposure

- 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



Daysimeter. Lighting Research Center, Rensselaer Polytechnic Institute.

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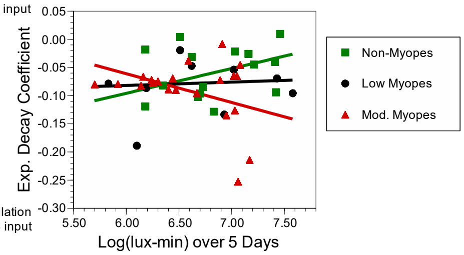
Refractive error by light exposure interaction

Slower Re-dilation
More ipRGC input

Faster Re-dilation
Less ipRGC input



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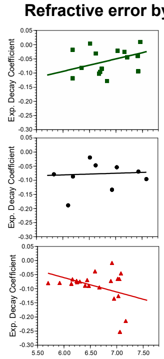
Refractive error by light exposure interaction

Slower redilation
More ipRGC input



Non-myopic
(>–0.50 D)

Low myopia
(between –0.50 D and –2.00 D)

Moderate myopia
(more myopic than –2.00 D)

Faster redilation
Less ipRGC input

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Refractive error by light exposure interaction

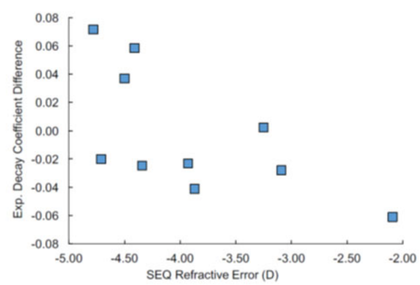
High Light
Enhancement

High 6.8 ± 0.2
Log lux-min

minus

Low 6.3 ± 0.3
Log lux-min

High Light
Inhibition



p-value = 0.009

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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.

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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.

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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 part 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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Acknowledgment

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  The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health

- NEI T35 EY007151

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