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by

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Abstract

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Refractive errors (e.g. nearsightedness or farsightedness) are the product of a mismatch between the axial length of the eye and its optical power, creating blurred vision. Uncorrected refractive errors are the second leading cause of world-wide blindness. One refractive error currently holding tremendous scientific interest is myopia (or near-sightedness), mostly due to its rising prevalence worldwide and associated ocular disease burden. That the increase in myopia prevalence has been rapid, occurring over a short period of time, suggests environmental influences in addition to genetic influences on eye growth. In this dissertation, the evidence for influences of genetic and environmental factors related to myopia development are presented as well as a discussion of the possible role of nutritional and body-metric factors through an analysis of NHANES data. Key environmental factors that have implicated in myopia development and/or progression relate to near work and outdoor activity, however traditional studies investigating these factors rely on subjective questionnaires. Possibly related to this limitation is the fact that no strong risk factors for myopia development have been described to date. The dissertation research presented here is novel in that it utilized objective technologies, including wearable technologies, to investigate the relationship between the dynamics of habitual indoor and outdoor behaviors, including the lighting characteristics experienced, to myopia presence and severity in young adult university students in both an academic and non-academic period.

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1. Myopia: Genetic and Environmental Influences

OVERVIEW OF REFRACTIVE ERRORS AND EMMETROPIZATION

The World Health Organization (WHO) ranks globally, uncorrected refractive errors as one of the top causes of vision impairment worldwide (44 percent), and in 2010, estimated there to be 285 million visually impaired people, of which 39 million were blind. Related figures from a recent review (Naidoo et al. 2016) reported that uncorrected refractive errors were responsible for moderate or severe visual impairment in 101.2 million people and blindness (visual acuity worse than 3/60) in 6.8 million people worldwide in the year 2010. To address this public health issue, the WHO drafted the global eye health plan 2014-2019, which in part, aims to secure access to eyecare services across the globe to reduce the incidence of avoidable visual impairment.

Almost every human eye has some level of refractive error, regardless of whether it is optically corrected with spectacles or contact lenses, or not. This review aims to summarize identified genetic and environmental influences on refractive error development, with a particular emphasis on those linked to myopia.

Etiology and Symptoms of Myopia

Refractive errors reflect a mis-match between the axial length of the eye and its optical power, resulting in blurred retinal images (Figure 1.1). This mis-match is commonly encountered in newborn infants, who frequently exhibit significant refractive errors, most of which resolve as the powers of the optical components, namely the cornea and intraocular crystalline lens, change with development and the eye elongates (Mutti et al. 1998, 2005; Zhu & Li 2009). This passive, emmetropization process is supplemented by an active visually-mediated emmetropization process by which residual refractive errors are eliminated (Wildsoet 1998, discussed further below). The presence of refractive errors in childhood represent failures of the latter emmetropization process.

The focus of this dissertation will be on one such refractive error, myopia or near-sightedness. Myopia is the product of the axial length of an eye being too long for its optical power. These eyes are relatively overpowered and thus distant objects come into focus in front of the plane of the retina; the result is maximally blurred vision of objects at far viewing distances and less blur at nearer viewing distances. Myopia may occur as part of a systemic congenital syndrome involving several bodily tissues, so called syndromic myopia. However, most myopia falls outside this category and is typically categorized according to its age of onset, i.e., congenital (present at infancy, often at high levels and especially in premature infants), pre-school, juvenile-onset or school (the most common form) and adult-onset. Juvenile- and adult-onset myopias are mostly axial in nature, the products of dysregulated growth mechanism(s). They do not hold the same high amblyogenic risk as uncorrected hyperopia, since it appears later and because uncorrected myopes generally experience clear vision at near distances. Nonetheless, myopia carries a significant risk of visual impairment, linked to retinal detachments, myopic maculopathy, glaucoma and cataracts, even when present only in low to moderate levels, although the risk is much greater in the case of high myopia (typically defined as worse than -6.00D; see reviews by Flitcroft 2012a, Saw et al. 2005).

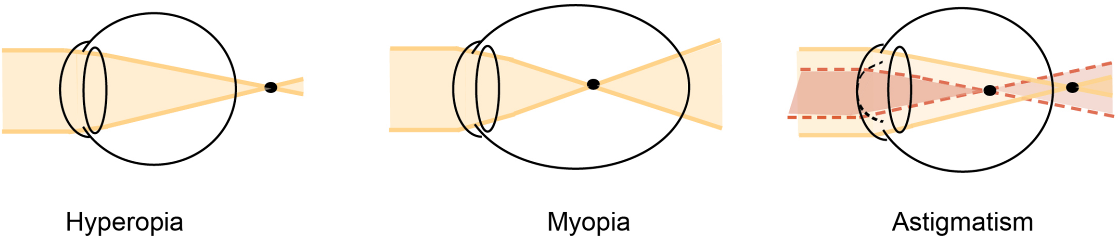

Figure 1.1: Schematic Diagram of Refractive Errors. *Hyperopia* (farsightedness) results from an eye having too little optical power for its shorter than average axial length, resulting in a focal point that is longer than the eye. *Myopia* (nearsightedness) results from an eye having too much optical power for its longer than average axial length, resulting in a focal point that is shorter than the eye. *Astigmatism* generally results from the front most optical element of the eye, the cornea, having a non-spherical curvature. The principal corneal meridians have non-identical powers, with one meridian being steeper (e.g. horizontal meridian, dashed corneal contour) than the other (e.g. vertical meridian, solid corneal contour), resulting in two focal points across the eye.

Emmetropization: A Visually-Guided Processes

Emmetropization describes the shift in refractive error from their neonatal starting point towards emmetropia. As alluded to above, ocular development alone, contributes to this process through a scaling effect, linked to eye enlargement and a reduction in the optical (dioptric) power of the eye (Sorsby et al., 1961). Neonatal infants exhibit a broad, near normal distribution of refractive errors, with a peak (average), of approximately +2.00 D hyperopia. This distribution quickly narrows and the peak shifts towards emmetropia over the first two years of life (Mayer et al., 2001) (Figure 1.2). While passive emmetropization can account for much of these early changes, a later active and visually mediated process is responsible for refining the balance between an eye's optical power and axial length to achieve emmetropia.

Several animal models showing that eye growth could be altered by visual manipulations, for example, by spatial form deprivation, provided the first evidence for the existence of active emmetropization (for a review see Wildsoet 1997). Clinical parallels include eyes deprived of 'normal' vision, e.g. due to congenital cataract or ptosis, where the emmetropization process also appears to fail (Kiorpes and Wallman, 1995; Rabin et al., 1981). Animal studies also point to active emmetropization being largely a local ocular process, with the retina responsible for both detecting and decoding defocus errors and generating growth-modulating signals to guide compensatory eye growth (for a review see Wallman & Winawer 2004). While these studies typically involve refractive errors artificially induced with defocusing lenses, it is likely that the same mechanism(s) underlies normal emmetropization. These studies have also provided important insights into the environmental factors that may underlie the development and progression of human myopia, which is discussed in a later section.

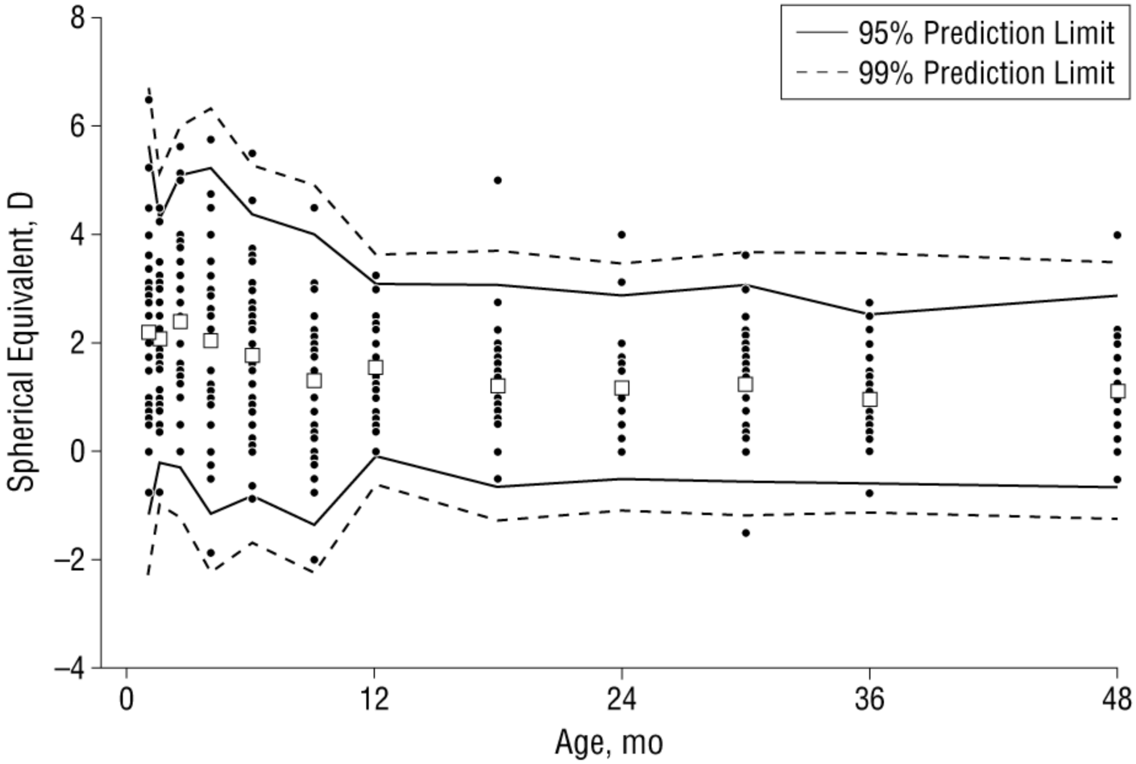

Figure 1.2: Cycloplegic Refractions in Children Aged 1 through 48 months. The distribution of cross-sectional refractive error data in infants is wide with an on-average refractive error of +2.0D of hyperopia, although the distribution narrows and moves towards emmetropia in the first two years of life through the emmetropization process. Originally published by Mayer et al (2001).

Prevalence of Myopia: Effects of Age and Ethnicity

A recent systematic review and meta-analysis (Hashemi et al., 2018) sought to estimate global and regional prevalence figures for the three main categories of refractive errors. For children across WHO-defined regions, the estimated pooled prevalence of astigmatism (14.9%, 95% CI: 12.7-17.1) was higher than that of hyperopia (4.6%, 3.9-5.2) and myopia (11.7%, 10.5-13.0). For adults, the prevalence of astigmatism was also higher (40.4%, 34.3-46.6) compared to that of hyperopia (30.9%, 26.2-35.6) and myopia (26.5%, 23.4-29.6). However, this study also found refractive error prevalence figures to vary greatly between countries, suggesting that genetic and/or environmental influences may play roles in refractive error development. That differences in ethnicity may contribute to such differences is also suggested by several epidemiologic studies, as discussed below. Notably, from 1990 to 2016, prevalence estimates for myopia have been trending upwards, by approximately 30%, while those for hyperopia have trended downwards, by approximately 10% (Hashemi et al., 2018).

Unlike the natural history of hyperopia and astigmatism, which both decline during early development, myopia may first appear around 6-8 years of age, although it is possible that it was also present at birth, to subsequently disappear and re-emerge. Myopes typically exhibit a fast phase of progression, followed by slowing and eventual stabilization at approximately 15-21 years of age (Hyman et al., 2013), although there is significant variability between individuals and ethnic groups in the age of onset of myopia and its subsequent evolution. Thus, there are several reports of myopia developing in young adults and/or myopia progression following periods of previous stabilization, typically in university students, suggesting that eyes remain susceptible to certain environmental influences, even when encountered later in life (Gilmartin, 1998; Kinge et al., 2000; Wildsoet, 1998). There are also reports, mostly from East Asian countries, of myopia developing in preschool years (Fan et al., 2004).

There has been a rapid increase in the prevalence of myopia worldwide and it is now projected to affect over 50% of the world's population by 2050 (Holden et al., 2016). In one US-based study, the prevalence of myopia was reported to increase in both men and women by 66.4% between 1971 and 2004 (Vitale et al., 2009), and another study involving a large, ethnically-diverse population reported an average prevalence rate of 26% in school-aged children (Kleinstein et al., 2003). The rise in the prevalence of myopia has been even more dramatic in East Asia, as evidenced by the results of several large-scale population-based studies and in a recent meta-analysis of 50 population-based studies across Asia, which reported a pooled prevalence of 47% in those aged 20-29 years compared to only 26% in those aged 50-59 years (Pan et al., 2012). Within the rural China cohort of another large-scale study utilizing cluster sampling to identify children 5-15 years of age across Chile, Nepal, and China (Refractive Error Study in Children, RESC study), myopia was essentially absent in 5-year olds, but was present in 36.7% of males and 55% of females by 15 years of age (Zhao et al., 2000). These trends are mirrored in those of MEPEDS (Multi-ethnic Pediatric Eye Disease Study), in which Asian children were also found to have both a slightly higher prevalence of myopia and lower severity of hyperopia compared to Non-Hispanic White children (Wen et al., 2013). Interestingly, the prevalence of myopia in Scandinavian countries has remained low, with a recent study from Norway reporting a figure of 13% for adolescents aged 16-19 years (Hagen et al., 2018).

In summary, there appears to be striking ethnicity-related differences in the prevalence of refractive errors. While genetic factors may contribute to such differences refractive error development, it is important to also recognize the potential role of shared environments, which may also vary with ethnicity, a topic taken up again later.

ROLE OF GENES

It is often observed that parents who wear glasses will beget children who wear glasses. However, one relevant study found that having two myopic parents only marginally increased a child's chance of becoming myopic, compared to having one myopic parent (Jones-Jordan et al., 2010). Thus, while such trends have been commonly attributed to genetic influences, other contributing factors are likely involved. The role of genetics in myopia development (and more generally, refractive error in some cases) has been studied via classical twin studies, genome-wide association studies (GWAS), and more recently in epigenetic studies. Syndromic myopia represents another avenue for investigating the biological pathways involved in ocular growth regulation, through which novel genes not previously identified via GWAS have been identified (Flitcroft et al. 2018).

Twin Studies

Initial observations related to the possible role of genes in myopia development come from twin studies. Classical twin studies assume a 100% match in the genetic profiles of monozygotic twins while dizygotic twins share approximately only 50% of their genes, while both share 100% of their environment. The first such study of refractive error found that the refractive errors of monozygotic twins to be more similar than those of dizygotic twins (Jablonksi, 1922). However, the reported rates of heritability of refractive error in twin studies vary widely, likely due to differences in sampling and analytic methods (Dirani et al., 2006); 30.6% (Tsai et al., 2009), 8-14% (Angi et al., 1993), 90% (Hammond et al., 2001). Relevant recent reviews also caution that more objective, longitudinal measures of eye length are needed to better understand the role of genes in eye growth (Dirani et al., 2006). Furthermore, it must be recognized that heritability estimates represent indicators of both environmental and genetic influences on the phenotypic variation in a population rather than the influences on an individual's phenotype (Chen et al., 2016). As a final cautionary note, it is also important to consider that classical twin studies assume a 100% match of environmental influences for *all* twins, potentially leading to an overestimation of heritability (Boomsma et al., 2002).

Genome-Wide Associated Studies

Recent advances in the ability to perform genome mapping has allowed for a better understanding of how variations in genetic and refractive error profiles correlate among individuals. Genome-wide associated studies (GWAS) probe the entire genome to identify single-nucleotide polymorphisms (SNPs) and their possible relationship to the presence of refractive error in an individual. Nucleotides represent the DNA building blocks. Among the studies impacting most on our understanding of the role of genes in myopia is a 2013 meta-analyses of GWAS data from two large data sets, 23andMe and the Consortium for Refractive Error and Myopia (CREAM).

Using a sample of 45,771 European participants, the DNA testing company, 23andMe, identified 22 significant loci associated with myopia, of which 20 were novel (Kiefer et al., 2013). The SNPs loci identified in this study suggest that a variety of ocular functions may contribute to myopia development; identified genes were variously linked to extracellular matrix formation (LAMA2), regeneration of 11-cis-retinal (RGR, RDH5), growth and guidance of retinal ganglion cells (ZIC2, SFRP1), and neuronal signaling or development (KCNMA1, RBFOX1, LRRC4C, DLG2, TJP2) (Kiefer et al., 2013). One limitation of this study is the reliance on questionnaires in determining the refractive error status of participants. It is thus plausible that significant refractive error misclassification occurred.

In contrast to the above 23andMe study, the CREAM group used objective measures of refractive error to classify participants. Analysis of data from 37,382 individuals of European descent and 12,332 of Southeast Asian ancestry (Verhoeven et al., 2013) linked 24 chromosomal loci to the presence of refractive error, with significant overlap between the two cohorts, suggesting shared genetic determinants for myopia development across these populations. Identified novel gene loci corresponded to a variety of functions, including neurotransmission (GRIA4), ion channels (KCNQ5), retinoic acid metabolism (RDH5), extracellular matrix remodeling (LAMA2, BMP2), and eye development (SIX6, PRSS56).

To date, GWAS studies have identified approximately 30 distinct susceptibility loci associated with myopia and/or refractive error. Nonetheless, these studies and other recent meta-analyses demonstrate that overall, genetic variations account for less than 12% of variations in refractive error (Fan et al., 2016; Kiefer et al., 2013; Verhoeven et al., 2013; Wojciechowski and Hysi, 2013).

Epigenetics

Altered gene expression and thus phenotype that do not reflect a person's DNA sequence (genotype), but instead, arise from post-translational modifications (e.g. through DNA methylation), represent epigenetic phenomena (Holliday, 2006). Such modifications may be the product of early environmental influences on the genome (Jirtle and Skinner, 2007). In the field of myopia, attention has only recently been paid to the role of epigenetics in its development, with the hope of shedding new light on myopiagenic risk factors.

As an example of the power of the above approach, the CREAM group recently performed a gene-environment-wide association analysis that considered the role of education (Fan et al., 2016). Interestingly, the interaction effects of education were found to be more strongly associated with the severity of myopia in Asian participants, compared to European participants, with this effect accounting for approximately -0.60 D more myopia in the former group. Three gene loci, AREG, GABRR1 and PDE10A, were found to significantly interact with the level of education. To rule out the possibility that the level of education represented a surrogate for near work activity, the interaction effects of near work were also analyzed, with only one significant association identified, involving the PDE10A gene (Fan et al., 2016).

Beyond Genetics

Juvenile myopia, the most common form of myopia, is considered a complex eye disorder. It is also very likely multifactorial, involving interacting genetic and environmental influences. As just summarized, while genetic factors appear to play a role in the development of myopia, it seems implausible that they alone could account for the recent dramatic increase in myopia prevalence. The visual environment and human behavior, to which it is intimately tied, likely hold clues to additional risk factor(s) for the development and/or progression of myopia.

ROLE OF VISUAL ENVIRONMENT

The role of the visual environment in myopia development has long been debated and the list of potential environmental influences studied, long. Nonetheless, our understanding of the environmental factors most strongly influencing ocular growth regulation and/or myopia progression remains poor, due in part to study design challenges (e.g., controlling for confounding factors, sampling method, etc.). A recent review of several worldwide population-based epidemiological studies identified as key environmental risk factors for myopia, limited outdoor activity and increased amounts of near work, yet it is not known whether these risk factors vary in their relative importance in different regions of the world (Ramamurthy et al., 2015). Reports of slower myopia during the summer months when presumably children are doing less near work and more outdoor activity, also offers indirect support for the above myopia risk factors (Cui et al., 2013; Fujiwara et al., 2012; Gwiazda et al., 2014). Since these factors have been the most heavily studied in relation to human myopia, they will be discussed in detail below, followed by a brief discussion of the other potential influences, which are often hard to disentangle from confounding factors.

Education/IQ

The first suggestion that something connected with education might be a risk factor for myopia development came from the classical epidemiological study of Alaskan Eskimo families by Young et al (1969). In relation to correlations between the refractive errors of parents and siblings in 41 family units (197 participants), the correlation among siblings was found to be highest, suggesting environmental influences. Moreover, while there was virtually no myopia in parents or grandparents, the prevalence of myopia in children was approximately 50%. The authors speculated that the advent of education and/or recent dietary changes for the population might be to blame. Anecdotal evidence has also long suggested a link between education and the development of myopia, and this association was confirmed in a large, more recently published study (Mirshahi et al., 2014).

As noted above, a gene-environment meta-analysis undertaken by the CREAM group also considered the interaction between education and genetic influences on myopia in those of Asian and European ancestry. The effect of education alone was found to be greatest for East Asian individuals, especially Singapore Chinese (β coefficient = 1.09), as compared to those of European descent (β coefficient = 0.49), although this difference is likely not clinically significant due to the substantial variability in the data. Interestingly, genes had a larger influence on Asian participants with higher levels of education compared to those with lower levels of education, suggesting epi-genetic influences (Fan et al., 2016); no significant interactions between SNPs and education were identified for European participants.

Higher intelligence, as defined by intelligence quotients (IQ), was first linked to be to myopia in 1883 by Cohn (Cohn, 1883). Nonetheless, contemporary studies have reported conflicting results. In the longitudinal Twin Early Development Study (TEDS), IQ alone was reported to explain only 1.5% of refractive error variance, despite an apparent shared genetic risk for IQ and myopia (Williams et al., 2017). This result contrasts with those from the earlier Avon Longitudinal Study of Parents and Children (ALSPAC), in which the odds of being myopic (defined as -1.50 D or worse, non-cycloplegic auto-refraction) between 7-10 years of age was significantly increased in those children with higher verbal or performance IQ scores (Williams et al., 2008). Challenges in teasing apart possible confounding environmental influences in these studies make it difficult to draw conclusions in relation to key causative and protective factors.

Near Work and Myopia

The apparent link between education level and myopia may reflect a confounding influence of the increased near work associated with educational activities. In addition, it has been hypothesized that reduced near work (possibly combined with an increase in outdoor activity) may be responsible for the apparent slowing in progression of myopia observed during the non-school, summer months (Fujiwara et al., 2012; Gwiazda et al., 2014; Tan et al., 2000). Reading and other near work activities are typically very dynamic processes and as such, there are likely a number of contributing myopiagenic factors, some possibly yet to be discovered. The amount of near work, accuracy of accommodation (a source of focusing errors), habitual working distance and gaze behavior could each contribute to the risk for myopia development, as discussed further below. Over the last few decades, increasing attention has been paid to the role(s) of these aspects of near work. To-date it has not been possible to identify one key causative risk factor related to near work, likely reflecting the use of artificial (lab-based) testing conditions and simple qualitative metrics traditionally used by investigators.

To provide a modern context, it is also important to recognize that the ‘near work’ performed by today’s children has evolved dramatically, to include device use, head-mounted displays and virtual/augmented reality. A recent survey (2017) by the non-profit Common Sense Media group (www.commonsensemedia.org) found that 49% of young children (8 years and less), ‘often or sometimes’ used a device in the hour before bedtime and were exposed to screen media for over 2 hours a day. Based on parental reports, infants (under 2 years) also had significant daily exposure (approximately 42 minutes) to screen media, up from 5 minutes per day, based on a 2011 survey. Regardless of whether this increased device use is partly to blame for the current myopia ‘epidemic’, because today’s children are not performing the same types of near work as the children of even a decade ago, the approach to studying near work as it relates to myopia must also evolve.

Potential Near Work Risk Factors

There are several potential near work risk factors that have been studied and some will be discussed in greater detail in Chapter 3. In general, the role that the *amount of near work* undertaken by a child plays in myopia development remains unclear. Challenges in deciphering results from relevant studies include the ‘definition’ of near work (e.g., reading, computer work, studying, etc.) and the metric used to quantify ‘amount’ (e.g. time, number of books typically read), both of which vary across studies. In addition, studies investigating the amount of near work sometimes involve hybrid metrics that take both working distance and time into account (e.g., diopter-hours), and gaze breaks (between periods of continuous fixation), factors, which on their own may represent risk factors, as discussed below.

As near work is one of the earliest environmental influences studied in relation to myopia, the body of literature is extensive and challenging to navigate. Two recent systematic reviews have been helpful in this respect. In one review, Ramamurthy et al (2015) summarized results from six key population-based epidemiological studies, all but one of which reported an association between increased amounts of near work and myopia. In the other review, Huang et al (2015) report results from a meta-analysis of 11 studies investigating the association of hours of near work and the presence of myopia; again, increased near work was found to be associated with myopia, albeit to a small, non-clinically significant degree (summary OR:1.14). The later review also covered three studies using the diopter-hours metric of near work and found no effect of increased diopter-hours of near work towards future myopia development. Finally, the mean hours of various near work activities (reading, watching TV, studying, playing computer/video games) were compared for myopes and non-myopes across all studies, with no clinically meaningful differences being found (mean differences approx. 30 mins or less).

Accommodative lag, or under-accommodation (for near targets), was alluded to earlier as a possible explanation for the apparent risk that near work conveys. With accommodative lags, the retina will experience hyperopic defocus, which has been shown in several animal species to trigger increased (myopic) eye elongation when imposed on normal eyes with defocusing lenses (reviewed in Wallman & Winawer 2004). However, no consistent trends are apparent in results from studies involving children, with some studies finding increased accommodative lags prior to the onset of myopia (Drobe and de Saint-André, 1995; Goss, 1991; Gwiazda et al., 2005) and others, increases after the onset of myopia (Mutti et al., 2006; Nakatsuka et al., 2005). In addition, no consistent relationship between lags of accommodation and myopia progression is evident in the results of three large clinical myopia trials (Berntsen et al., 2011; Gwiazda, 2011; Koomson et al., 2016) and another longitudinal study (Weizhong et al., 2008). While these inconsistencies may reflect the non-natural testing conditions and methodological inconsistencies (e.g., testing with habitual vs. full spectacle correction, non-habitual working distance, non-sustained task, etc.), no conclusion can be made in relation to the role of accommodative lags as a myopia risk factor based on current data.

Given that the accommodation and vergence systems are intimately linked neurally, it may be more appropriate to consider both systems together rather than individually. There are at least two pieces of evidence that support this approach: 1) progressive addition lenses (PALs), used as myopia control treatments, appear to be more effective in those children with large lags of accommodation and near esophoria (Gwiazda, 2011), and 2) near addition lenses with base-in prism incorporated to reduce both accommodative and vergence demands appear to be more effective at controlling myopia progression compared to near addition lenses without prism for children with lower lags of accommodation (less than <1.01 D) (Cheng et al., 2014).

Close near working distances and *gaze breaks* having both been suggested as a possible risk factor for myopia development and progression were investigated as part of this dissertation research and will discussed in greater detail in Chapter 3.

Retinal Defocus Patterns

It is well-accepted that eye growth regulation is a local (ocular), visually-mediated process, a theory that has as its foundation, decades of animal studies (for a review see Smith et al. 2014). The local nature of this process is probably best evidenced by the fact that an eye isolated from the brain by optic nerve section still responds to myopiagenic stimuli (e.g., form depriving diffusers and negative lenses) and axially elongate (Schmid and Wildsoet, 1996; Troilo et al., 1987; Wildsoet and Pettigrew, 1988). That local, regionally specific myopia-generating stimuli induce asymmetric ocular growth patterns represents further indirect evidence of local ocular growth regulation (Diether and Schaeffel, 1997; E. L. Smith et al., 2009a). For the primate eye and so presumably humans, there is further evidence that the peripheral retina plays an important in decoding blur and initiating the signaling cascade for ocular growth, as opposed to the foveal region alone (for a review see Wallman & Winawer 2004). Thus, it is perhaps better to consider the ‘global’ retinal experience when considering influences on ocular growth. As noted earlier in discussion of accommodative lags, hyperopic defocus (plane of focus behind the retina) appears to trigger a ‘grow’ signal while myopic defocus (plane of focus in front of the retina) triggers a ‘stop’ signal and is the foundation for optical myopia control treatments such as ortho-keratology lenses and multi-focal contact lenses which modify the defocus patterns of the peripheral retina (for a review see Walline 2016). As an alternative, in theory if an individual were able to surround themselves in a visual environment that reduces or eliminates hyperopic defocus on their peripheral retina alone, their risk of myopia development and/or progression would be reduced. Insight into how indoor and outdoor environments differ in their myopia-genic properties is provided by defocus models included in the review paper by Flitcroft (2012) and depicted in Figure 1.3. Hyperopic retinal defocus is more frequently encountered indoors than outdoors, as objects nearer than the fixation distance are more likely encountered in this more crowded environment and for this reason, indoors environments are predicted to be also more myopiagenic. Moreover, that myopes may spend more time fixating on their near work without fixation breaks, at closer near working distances, will only further exacerbate the problem.

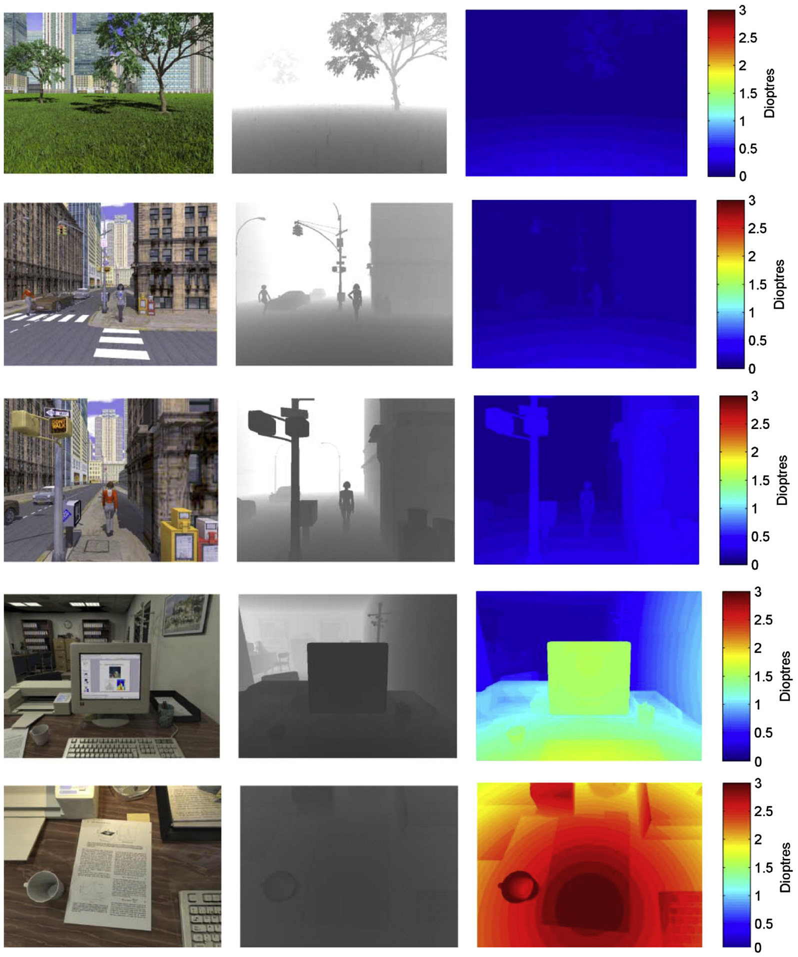

Figure 1.3: Dioptric Variation in Indoor and Outdoor Visual Scenes. The first column depicts rendered images of outdoor and indoor visual scenes, the second column represents a grey scale depth image of the same scenes, relative to the eye, with the brighter intensities representing further distances (in meters), and the third column represents the dioptric transformation of the respective scenes where cooler colors represent less diopters. In general, indoor visual scenes have more dioptric variation compared to outdoor visual scenes as indicated by the associated dioptric heat maps. Adapted from original publication by Flitcroft (2012).

Outdoor Activity and Myopia

The finding from the Sydney Myopia Study that children reporting low levels of outdoor activity combined with high levels of near work had the highest odds of being myopia (Rose et al., 2008) has served to draw sustained attention around the world to the possible protective effect of outdoor activity on the development and/or progression of myopia. Since that study, a plethora of related cross-sectional and cohort studies have been published along with four randomized control trials (RCTs, in Asia) investigating the possible protective effect of increased outdoor time.

Differences in design, including the lack of consistency across relevant studies in how outdoor exposure is quantified, make comparisons across studies difficult and interpretation of collected data challenging. In fact, a recent systematic review of the methods used to measure time outdoors in myopia research involving child concluded that more integrated and objective methods are needed (Wang et al., 2018). As just one example, many studies have relied on either or both self and parental reports to estimate time spent outdoors. There are also inter-study differences in the criteria used to characterize outdoor exposure; for example, in some but not all studies, sports and time spent outdoors have been grouped together (Dirani et al., 2009), weekend and weekday activities distinguished (Guggenheim et al., 2014), and leisure outdoor activities and sporting activities separated into distinct categories (Jones et al., 2007).

One of the first meta-analysis of relevant literature (involving 7 cross-sectional studies) reported that increased time outdoors conferred a protective effect, equal to an approximate 2% decrease in odds for a weekly increase in exposure of 1 hour (Sherwin et al., 2012). A review of 5 prospective studies in the same paper found myopes to engage in significantly less outdoor activity compared to non-myopes (7.68 vs. 11.65 hours/week, respectively), with a 9% reduction in the odds of developing myopia for every 1 hour increase in outdoor activity per week.

Additionally, a recent meta-analysis of cohort studies investigating the role of outdoor activity and myopia development found the protective effect of outdoors to be more robust in younger compared to older children (aged 6 vs. 11-12 years) (Xiong et al., 2017). Of longitudinal cohort studies involving school-aged children, the ALSPAC group reported an approximate 10% reduction in the hazards ratio of myopia (as measured by non-cycloplegic autorefraction) for each hour of increased outdoor activity per day (Shah et al., 2017), with an equivalent effect on ocular dimensions reported in the Beijing Children Eye Study, with increased time outdoors associated with reduced axial elongation over a 4-year follow-up period (Guo et al., 2017). Finally the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error study (CLEERE) found reduced time outdoors to be associated with the future development of myopia (Jones-Jordan et al., 2011).

Recent Randomized Control Trials of Outdoor Exposure

To-date, four randomized control trials (RCTs) have been completed, all in East Asia (China and Taiwan), where the myopia problem is most severe. Each of these studies used a similar cluster-randomization design at the school level (He et al., 2015; Jin et al., 2015; Wu et al., 2013), and all studies also used similar interventions, i.e., of increased time outdoors of 40-80 additional daily minutes, although the dosing strategies differed. The dose of outdoors was provided as one interval in one study (He et al., 2015) and distributed across multiple intervals in the other two studies (Jin et al., 2015; Wu et al., 2013). The results of these trials are summarized in Figure 1.4. Similar effects were found in all three cases; overall, increased time outdoors reduced myopia incidence by approximately 5-10% while having little to no effect on myopia progression (or axial elongation) in already myopic children (at baseline). Results of a recent meta-analysis of these and other related studies also found no dose-response relationship between time outdoors and myopic progression in myopic children (Xiong et al., 2017).

To further investigate the protective effect of outdoors observed in the Taiwanese study, researchers initiated a follow-up RCT in which participants wore a light sensor device around their necks during the school day (Wu et al., 2018). In addition, and different from the preceding study, children receiving myopia control treatments were excluded. This group accounted for about 20% of the cohort in the earlier study and their exclusion lead to a substantial reduction in the number of already myopic participants (n=73/693). Nonetheless, a reduction in myopia incidence was again observed, albeit smaller than previously found (3% vs. 10%), and the effects on myopia progression and axial elongation over the 1-year study period were also small (0.23 D and 0.15 mm less, respectively). As will be discussed in further detail in Chapter 4, no significant differences in light exposure patterns (minutes of exposure to various light levels), existed between the groups, either at baseline or at the end of the study either at baseline or at the end of the study.

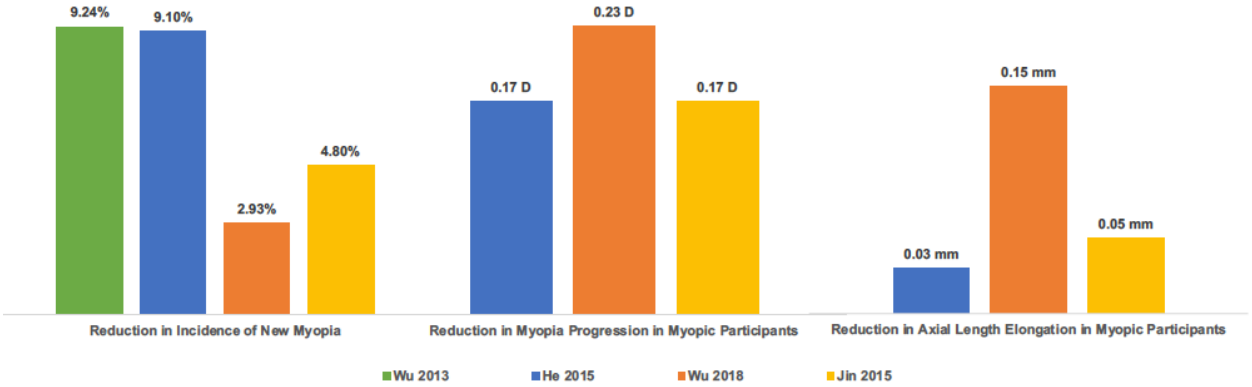

Figure 1.4: Summary of Results from Four Randomized Controlled Trials (RCTs) Investigating the Effects of Increased Outdoor Recess Time as a Myopia Controlling Intervention in Asian Schoolchildren. All four RCTs investigated the effects of increased outdoor recess time compared to a traditional school day (control). Bar graphs show effects of interventions expressed as change over the trial period in intervention group, expressed as percentage of change in control, in response to the interventions over the 1-year trial (Wu & Jin) or 3-year trial (He) periods. All studies reported relative reductions in myopia incidence, albeit variable across studies, while myopia progression and axial length elongation were minimally controlled in those children already myopic at baseline (no data reported by Wu 2013).

Possible Protective Factors

What aspect(s) of the outdoor environment are responsible for its observed protective effect against myopia remain to be determined. Potential contributing factors can be separated into lighting characteristics, activities and visual experience. While the former two have received significant attention more recently, little attention has been paid to the features of the outdoor visual experience, despite suggestions from experimental animal research that it may be important (Hess et al., 2006; Smith et al., 2014).

In relation to *outdoor activities,* attention has focused on the nature and amount of physical activity, yet neither appears to be critical to the protective effect of outdoors based on results from both subjective and objective studies (Guggenheim et al., 2012; Suhr Thykjær et al., 2017) (Read et al., 2014). While one pediatric longitudinal study (CLEERE) did report an association between lower levels of outdoor/sports activities and an increased risk of developing myopia in children (Jones-Jordan et al., 2011), it is difficult to disentangle physical from other outdoor activities in most studies.

Less-Implicated Environmental Influences

Parental smoking, in particular maternal smoking during pregnancy, has been linked with a reduced prevalence of myopia and shorter axial length in offspring compared to children of nonsmoking mothers. Specifically, three of four large population-based studies (based in the US, Egypt and Singapore) reported a significant association between parental smoking and hyperopia (Borchert et al., 2011; El-Shazly, 2012; Iyer et al., 2012) while the outlier, a UK-based study, reported an association between parental smoking and high myopia (Rahi et al., 2011). However, a recent review of these studies by Ramamurthy (2015) raised concerns about a general lack of control across studies for confounding factors, such as parental education, income, socio-economic status and myopia status.

Maternal age (greater than 35 years) has been linked with an increased odds of having myopic offspring. However, studies on this topic are limited and results inconsistent, with some finding a small increase in the odds of myopia (<1.10) (Rahi et al., 2011; Rudnicka et al., 2008) and others finding no association (Borchert et al., 2011). Also as with maternal smoking, older mothers tend to have babies of lower birth weight (Dennis and Mollborn, 2013), which has been associated with increased myopia (Rahi et al., 2011).

Birth order has been suggested as a risk factor towards myopia, although no well-defined hypothesis is available. A meta-analysis of four large epidemiological studies represents the most comprehensive examination of the effect of birth order (Guggenheim et al., 2013) and revealed a small but variable increase in myopia prevalence in first born children compared to other children. However, there are several confounders that are present typically in first born children (e.g., low birth weight, insulin resistance secondary to increased post-natal growth, higher education attainment) that could be responsible for this small effect of birth order (Ramamurthy et al., 2015). It is important also to note that none of the studies were designed to explicitly investigate the role of birth order and they have other limitations, including non-cycloplegic methods for collecting refractive error data, which may have led to misclassification of myopia.

Season of birth has been used as a marker for perinatal light exposure patterns in studies pursuing the hypothesis that diurnal light-dark cycles, which are known to influence the retinal melatonin–dopamine balance, may also influence emmetropization, as suggested by animal studies (for a recent review on the role of circadian rhythms in eye growth see Chakraborty et al. 2018). Thus, myopia prevalence is predicted to vary across season of birth. Two studies investigating this influence found birth in the summer to be associated with a small increase in the odds (<0.24) of having more severe myopia than in winter (Mandel et al., 2008; McMahon et al., 2009). In a third study, children born in the winter months showed clinically insignificant myopic shifts in their largely hyperopic refractive errors (based on non-cycloplegic auto-refraction), as compared to those born in summer months (Ma et al., 2014). In interpreting these results, it is also important to consider that in general, more babies are born in the summer months and that the season of birth also has a number of potentially influential confounders (e.g. parental education).

The possible link between Vitamin D levels and refractive error development in relation to outdoor exposure will be the focus of Chapter 2. Interestingly, the season of birth has also been considered as a marker for exposure *in utero* to Vitamin D, with important implications for later development. For example, a large UK Biobank study (n=450,000) found those born in summer months to have higher birth weights, later pubertal development and were taller as adults (Day et al., 2015). Interestingly, there is independent evidence linking eye length with body height, albeit independent of refractive error (Wang et al., 2011; Zhang et al., 2011). Also arguing against a protective effect of Vitamin D against myopia development, children born during the summer months with longer daylight, should have a reduced risk of being myopic, which is inconsistent with two of reports discussed above.

Finally, in the context of myopia risk factors, interest in *nutrition* stems from the observed increase in myopia prevalence with the "westernization" of native populations and countries. This will be investigated further in Chapter 2 but briefly, Cordain et al. proposed that diets of high glycemic load as a risk factor for myopia, further suggesting that hyperinsulinemia associated with high glycemic load may modify scleral growth factors, as an explanation for the link with myopia (Cordain et al., 2002).

The Visual Environment and Myopia - Questions Yet Answered

A significant deficiency in studies attempting to quantify the habitual visual environment of individuals has been the reliance on subjective reports, which are well recognized to be inaccurate (Alvarez and Wildsoet, 2013; Chan et al., 2016; Ostrin et al., 2018) and limited in their ability to capture potentially critical details such as the spatial and temporal pattern (dosing) of exposure, which has proven influential in animal studies (Backhouse et al., 2013; Lan et al., 2014; Nickla et al., 2017; Nickla and Totonelly, 2016). These deficiencies, among others, may be the reason why, to-date, no consistent risk factors for myopia development and protection from it have emerged and further suggest that key aspects of indoor and/or outdoor environment experiences have been missed. A primary focus of this dissertation's research (as described in Chapters 3 and 4) was to focus on quantifying habitual human indoor and outdoor behaviors as a step forward in better understanding the role of the visual environment in myopia.

CONCLUSION

In summary, uncorrected refractive errors are a leading cause of visual impairment around the world and myopia specifically is rapidly increasing in prevalence, especially in East Asia. In relation to myopia specifically, neither genetic nor environmental influences alone can account for the rapidly changing prevalence statistics and there are hints that certain indoor and outdoor behaviors are important (Figure 1.5). Slow progress towards a comprehensive understanding of the factors underlying eye growth regulation and refractive development in humans can be at least partly attributed to the reliance on insensitive subjective tools in related research. Advances in technology are changing this picture, as suitable tools are deployed along with suitable analytics to capture objective data on childhood indoor and outdoor behaviors, leading to an improved understanding of the factors underlying the development of myopia. In fact, a significant portion of the work presented within this dissertation focuses on the use of wearable technologies to better characterize the habitual indoor and outdoor activities of young university students and how they may relate to the presence and magnitude of myopia. Therefore, more informed, evidence-based clinical recommendations aimed at curbing the rapid rise in myopia prevalence can be expected, with behavioral modifications which potentially also integrate technologies.

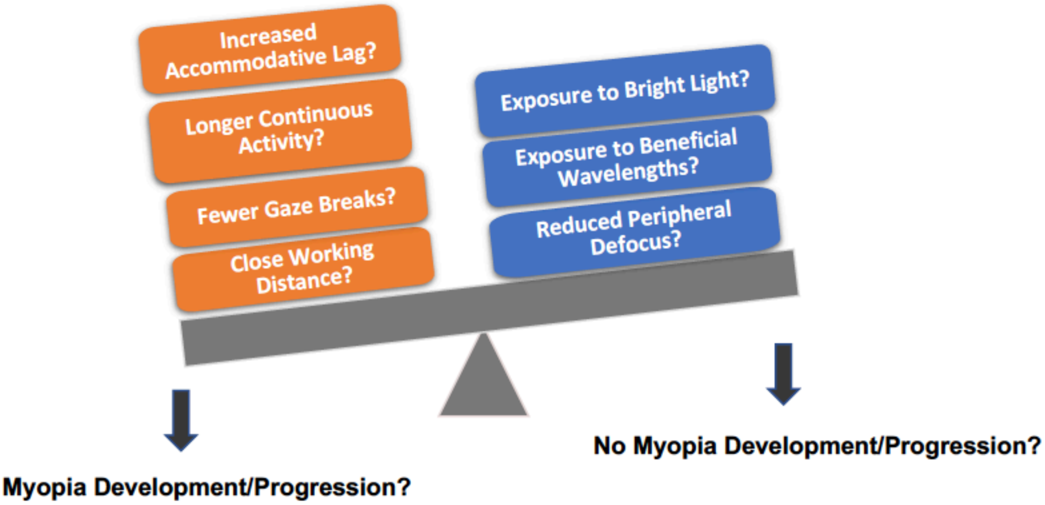

Figure 1.5: A Model of Human Myopia Development. This figure depicts the opposing influences of near work-related risk factors (orange) and outdoor activity-related protective factors (blue) as it relates to myopia development (incident myopia) and/or its progression, based on current evidence from basic (animal model) and human studies and conjecture based on indirect evidence, where relevant data are not yet available.

2. Nutritional Factors and Myopia : An Analysis of NHANES Data

INTRODUCTION

As introduced in the previous chapter, myopia has seen a rapid rise in its prevalence world-wide, such that half of the world's population is expected to be myopic by 2050 (Holden et al., 2016). Linked to this disease is a significant economic burden (approx 268 billion US dollars) (T. S. T. Smith et al., 2009), as well as a sight-threatening ocular disease burden (Flitcroft, 2012), a byproduct of the underlying excessive axial eye 'growth'. While genetic factors appear to play a role in the development of myopia (Chen et al., 2016; Dirani et al., 2006; Fan et al., 2016; Sherwin and Mackey, 2013; Wojciechowski and Hysi, 2013), as reviewed in the previous chapter, they cannot account for the dramatic increase in myopia prevalence over such a short period of time.

Several environmental factors have been implicated in the development and/or progression of myopia (for a review see Chapter 1); however, no general agreement has been reached on key factors and it likely will prove to be multi-factorial. Early epidemiological studies of myopia noted an apparent link between the advent of formalized classroom education and the development of myopia in Inuit populations (Morgan and Munro, 1973; Young et al., 1969). Several nutritional factors also underwent modification during this period of increasing Western influence (Cordain et al., 2005, 2002). Although relevant studies are sparse, some of these nutritional factors have also been explored in more recent ones as described in Chapter 1. Briefly, diets of high glycemic load were proposed as a risk factor for myopia by Cordain et al. who speculated that hyperinsulinemia might modify scleral growth factors, as a possible underlying mechanism (Cordain et al., 2002). However, in a cross-sectional study of Singaporean children (aged 7-9 years) (Saw et al., 2002) shorter stature and increased body mass index were associated with less myopic refractions, in apparent contradiction of the latter hypothesis, assuming BMI reflects glycemic load. On the other hand, recent studies using animal models of myopia have provided evidence for protective effects of both caffeine and one of its metabolites, 7-methylxanthine, against myopia development (Hung et al., 2018a; Nie et al., 2012; Trier et al., 1999), with choroidal and scleral targets under consideraton as possible sites of action (Trier et al., 1999).

As a possible protective factor against myopia development, significant attention has been paid more recently to outdoor exposure (for a review see (Xiong et al., 2017)). However, what aspect(s) of outdoor activity is(are) responsible remain to be determined, with potential contributing factors including lighting characteristics, visual experience and the nature of activities. While there is on-going debate regarding the possible protective role of high light intensities, as experienced outdoors, it is also important to note that exposure to sunlight and serum Vitamin D levels are highly correlated. Related, a case-series of myopic children treated with Vitamin D published in 1938 (Laval 1938), is perhaps the first to investigate its effect on eye growth. More recently, Vitamin D levels were reported not to be associated with myopia in a small Caucasian sample in a series of cross-sectional studies, although polymorphisms in the

Vitamin D receptor were found in low to moderate myopes(Mutti et al., 2007; Mutti and Marks, 2011). Most notably, is that fact that three relevant large cohort studies reached diverging conclusions with respect to the role of low serum Vitamin D levels as a risk factor for myopia development (Choi et al., 2014; Guggenheim et al., 2014; Tideman et al., 2016).

The availability of the large US National Health and Nutrition Examination Survey (NHANES) dataset allowed for further investigation into the relationship between various nutritional and body metric factors and the presence and magnitude of myopia, which describes the scope of the study reported here. NHANES comprises a series of ongoing studies, which was initiated in 1960 by the U.S. Centers for Disease Control and Prevention (CDC), and aims to investigate the health and nutritional status of children and adults across the United States through the collection of data concerning demographic, socioeconomic and health-related variables (via physiological and laboratory measurements).

METHODS

Study Cohort

The study reported here was limited to participants during study years 2003-2008. As refractive error data are only available for participants aged 12 years or older, the current analysis was limited to participants aged 12-25 years of age, with the upper limit taking into account the possible later onset of myopia (Grosvenor and Scott, 1991; McBrien and Millodot, 1987; Rahi et al., 2011). The number of participants included in the final analysis was 6913, with 30% (n=2091) of participants having complete datasets as described below. An initial investigation of the un-weighted demographic features of the individuals in the 2003-2008 dataset (Table 2.1) revealed the subject pool to be well balanced by sex (50% female) and age, and also quite ethnically diverse, as reflected in the repesentation in each of the four categories used (Whites, Blacks, Mexican Americans, Other Hispanics, and Multi/Other), although there were fewer participants in both the Multi/Other and Other Hispanic categories. These participant cohort features remained similar following the application of ethnicity weighting factors to allow findings to be generalized to the US population (Table 2.1, see also data analysis).

All study sampling methods pertaining to the NHANES data set have been described elsewhere (CDC/National Center for Health Statistics, n.d.). Pertinent to the analyses reported here, open-source data were extracted regarding participant demographics (age, sex, race/ethnicity), refractive error, vitamin D serum levels, daily caffeine intake, fasting glucose and insulin serum levels, and standing body height and BMI. Specifics about each data variable, which were all collected by NHANES trained health technicians, are described below.

Participant Characteristics	Un-Weighted (n=6,913)	Weighted (N=163,730,067)
Female Sex	3,464 (50.1%)	49.4%
Ethnicity		
Non-Hispanic White	2,145 (31.03%)	63.5 %
Non-Hispanic Black	2,127 (30.77 %)	14.13 %
Mexican American	1,962 (28.38 %)	11.67 %
Other Hispanic	381 (5.51 %)	5.11 %
Multi/Other	298 (4.31 %)	5.59 %

Table 2.1: Participant Characteristics. Summary of un-weighted and weighted participant demographic characteristics, expressed in terms of participant numbers and/or percentage of total population. The mean age of the unweighted and weighted populations was similar (17.1 vs. 18.4 years)

Databases

The *vision* database includes objective auto-refractor (Nidek ARK-760) measurements. Reliability measures for these refractive error data were obtained for all auto-refractor measurements and data only included when a confidence rating of at least 5 (scale from 1 to 9) was achieved. The mean (s.d.) confidence rating of the refraction data utilized in our analyses was 8.86 (0.43); participants were also excluded from analyses if they had more than 1.5 D of astigmatism. For the purpose of this study, spherical equivalent refractive errors (SERs) were calculated from the data for the right eyes of all included participants, and SERs of -0.75 D or worse were classified as myopic. The latter, more conservative definition was employed to avoid mis-classification of myopia, given that cyclopegic agents were not used in measuring refractive errors.

To monitor childhood growth and weight gain, NHANES collected a series of body metrics, including *body mass index* (BMI, kg/m^2) and *standing height* (height, cm). Within the NHANES laboratory database, 25-hydroxy *Vitamin D* serum levels (total 25 (OH) Vitamin D, nmol/L) were measured using a standardized liquid chromatography-tandem mass spectrometry method. Information about *caffeine* intake was extracted from the extensive dietary interviews performed as part of the ‘What We Eat in America’ initiative. Using a validated US Department of Agriculture (USDA) survey method, participants were initially interviewed in-person during a study visit and subsequently by phone (3-10 days following the in-person interview, but not on the same day of the week). During both interviews, participants were encouaged to make use of a set of measuring guides (e.g. glasses/mugs, bowls, drink boxes and bottles, household spoons, measuring cups and spoons) to more accurately estimate the amounts of foods and liquids consumed. The databases includes entries for 63 nutrients/food components, calculated from interview data using the USDA's Food and Nutrient Database for Dietary Studies. For the purpose of the current study, daily caffeine intake data (in mg) for each of the two interviews were averaged for each participant. Also included in analyses reported here were fasting (at least 9 h) plasma *glucose* (hexokinase method, mmol/L) and serum *insulin* (ELISA method, pmol/L), which were obtained for participants 12 years and older attending morning study visits, as part of an ongoing effort by NHANES to estimate the prevalence of Diabetes in the US.

Data Analyses

To allow our results to be generalized to the US population, all analyses, including multi-variate modeling, were weighted according to ethnicity, using the representative two-year weighting values provided by NHANES for each study period. Analyses were performed using Stata 14.2 (StataCorp, College Station TX USA). Graphical and weighted statistical analyses (Adjusted Wald Test) were initially performed to investigate the relationships between refractive errors, demographic factors and various nutritional factors. Multivariable logistic and linear regression models were created using SER, myopia status (present or absent) and magnitude of myopia as outcome variables, to investigate whether identified co-variates were related to overall refractive error, presence of myopia and/or the magnitude of myopia (in diopters). The inclusion of covariates in the final model was hypothesis-driven and effect modification was evaluated across all covariates; interaction terms were included in the final model when their coefficients differed significantly from zero, as determined by a Wald test. Given the large sample size, an alpha value of 0.01 or less was used in all data analysis as an indicator of statistical significance. Summary statistics are reported as weighted means, including standard errors and/or 95% confidence intervals, unless indicated otherwise.

RESULTS

Demographic Factors and Myopia Status

The participants included in analyses recorded a wide range of refractive errors, extending from +8.5 D of hyperopia to -20.25 D of myopia, with the mean falling in the range of low myopia (-0.94±0.04 D). The overall prevalence of myopia in the population was 34.3%, with the mean SER for myopic participants being -2.67±2.08 D and the mean SER for non-myopic participants, 0.12±0.74 D. Although both race/ethnicity and sex appeared to infuence refractive errors for the weighted population, as summarized in Figure 1, differences did not always reach statistical significance. Specifically, females had a higher prevalence of myopia compared to males (39.5% vs 33.4%, p=0.0014) and they were also significantly more myopic compared to males (-3.00±0.08 vs. -2.65±0.08 D) (p=0.007). The four different ethnic groups recorded relatively similar mean refractive errors, except for the Multi/Other group, which was more myopic (-1.66±0.20 D). Nonetheless, there was a significant difference between these groups in the prevalence of myopia (p=0.001), with Blacks recording the lowest prevalence (37.5%) and the Other/Multi group, the highest prevalence (59.4%). The magnitude of myopia also differed significantly across these groups (p=0.003), with Mexican Americans recording the lowest average myopia (-2.48±0.08 D) and the Other/Multi group, the highest (-3.32±0.28 D).

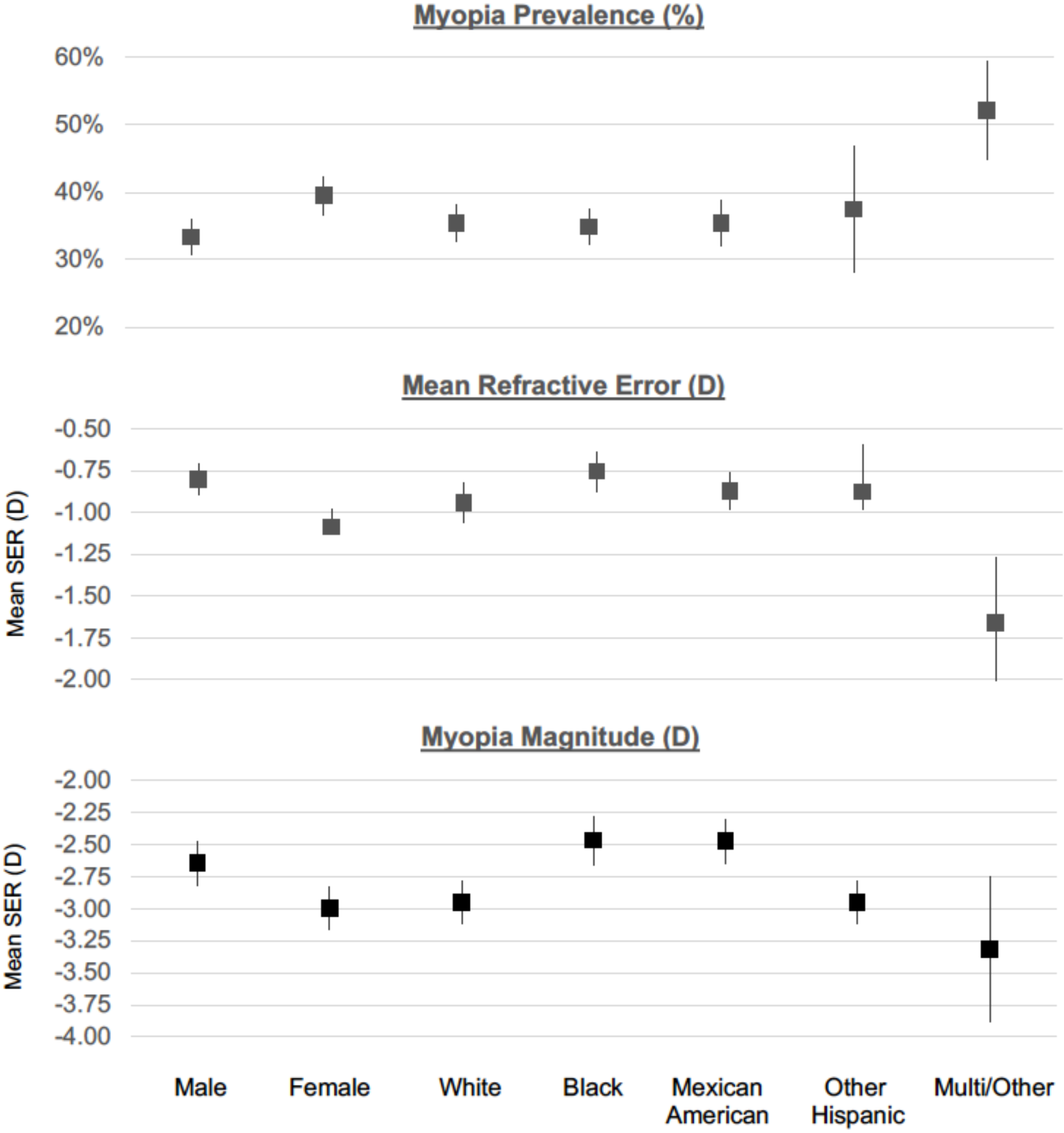

Figure 2.1: Refractive Error Characteristics of Participant Cohort. Myopia prevalence (top), overall spherical equivalent refractive error (middle) and myopia magnitude in those participants that were classified myopic (bottom), by sex and ethnic group. Data presented as means with 95% confidence intervals.

Body Metrics, Nutritional Factors & Myopia Status

Summary statistics for all biometric and nutritional factors, partitioned by participant demographic charateristics, are shown in Table 2.2 and described individually below. The average height of participants who had both refractive error and body metric data (n=6858, 99%), was 167.82±0.21 cm and their average BMI, 24.84±0.15 kg/m^2. Notably, the latter value is just outside the range for overweight as defined by the United States Centers for Disease Control and Prevention (25.0 to <30 kg/m^2; www.cdc.gov). Female participants had similar BMIs compared to males (25.70±0.20 vs. 24.70±0.15 kg/m^2 (p=0.15)), but were significantly shorter than males (162.21±0.15 vs. 173.24±0.25 cm (p<0.0001)). Ethnicity significantly influenced height (p<0.0001), but not BMI (p=0.108). In relation to height, Whites were the tallest (169.17±0.25cm) and Mexican Americans, the shortest (163.62±0.25cm). In relation to BMI, Blacks recorded the highest values, with their mean BMI falling within the overweight range (26.34±0.26 kg/m^2), and the Other/Multi group, the lowest values (22.90±0.46 kg/m^2). However, neither of these parameters, i.e., height and BMI, was significantly correlated with SER (Figure 2.2, both $R^2 \leq 0.0002$, $p \geq 0.42$).

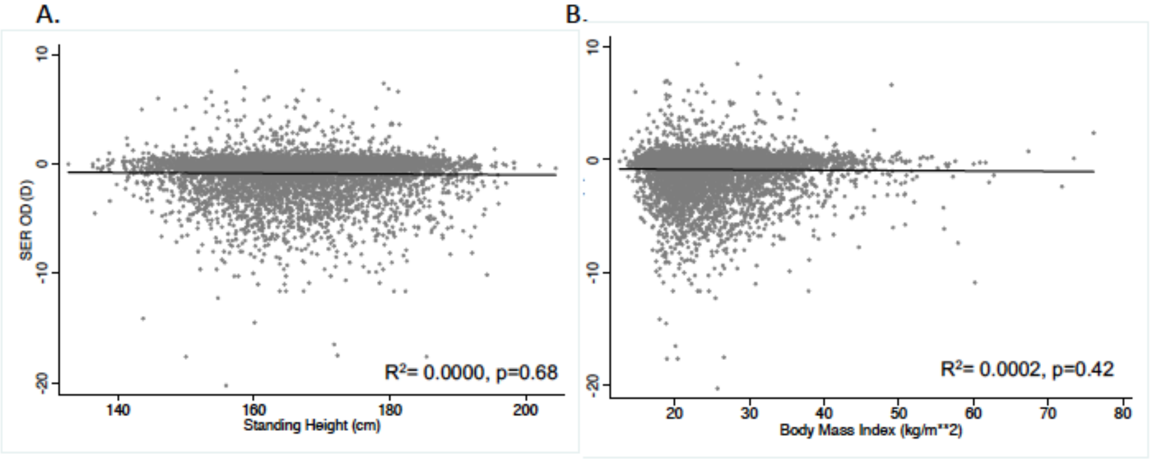

Figure 2.2: **Body Metric Factors and Refractive Error.** Relationship between standing body height (A) and body mass index (B) to spherical equivalent refractive error (SER, D). There was no significant correlation between either of the body metrics and SER in the study population.

A total of 4,884 participants had both serum *Vitamin D* and refractive error data. The mean serum Vitamin D levels for these participants was 62.78± 1.38 nmol/L, with a large proportion (~45%) of them classifiable as deficient in Vitamin D, as defined by the Vitamin D Council (below 50 nmol/L, www.vitamindcouncil.org). While females and males recorded similar serum Vitamin D levels (63.63±1.76 vs. 61.98±1.29 nmol/L, p=0.234), there were ethnicity-related differences that just met statistical signifcance, with Blacks recording the lowest levels (40.28±1.05 nmol/L) and Whites, the highest (71.14±1.41 nmol/L) (p=0.011). However, myopic and non-myopic groups recorded similar serum levels of Vitamin D levels (62.02±1.44 vs. 63.22±1.45 nmol/L, p=0.204), which is also reflected in the nonsignificant correlation between serum Vitamin D levels and SERs for this population (Figure 2.3a, R^2= 0.0003, p=0.34).

For participants who had both *caffeine* intake and refractive error data (n=6,012), the mean daily caffeine intake was 69.00±1.85 mg. Males recorded slightly higher caffeine intake compared to females (77.28±2.89 vs. 60.84±2.51 mg, p=0.0001), and there were also significant ethnicity-related differences in caffeine intake, with Blacks having the lowest intake (34.30±2.17 mg) compared to all other ethnic groups (all p-values ≤ 0.01) and Whites the highest (81.63±2.49 mg) compared to all ethnic groups except the Mixed/Other group (p<0.0001). However, there was no significant difference in the caffeine intakes of myopic and non-myopic participants (69.29±3.14 vs. 68.83±2.32 mg, respectively, p=0.91) and no significant correlation between caffeine intake and SER for this population (Figure 2.3b, R^2= 0.0002, p=0.54).

For participants who had both fasting serum *glucose and insulin* levels and refractive error data (n=3,021), their mean serum glucose level was 5.21±0.02 mmol/L and their mean insulin level was 72.24±1.69 pmol/L. Interesting, males had significantly higher glucose levels than females (5.35±0.36 vs. 5.04±0.02 mg, p<0.0001), but had lower insulin levels, which bordered statistical significance (68.98±2.46 vs. 76.01±2.16 mg, p=0.032). Serum glucose levels varied significantly with ethnicity, with Blacks having the lowest levels (5.08±0.04 mmol/L) compared to Mexican Americans, who had the highest levels (5.34±0.05 mmol/L, p=0.0003), although this difference is likely not clinically meaningful. Serum insulin levels also showed signifcant ethnicity-related differences, with the Other/Multi group recording the lowest levels (60.34±4.37 pmol/L, compared to all groups except Whites, p≤0.01), and Blacks the highest (82.95±3.33 pmol/L, compared to Other/Multi and Whites, p≤0.002). On average, myopes tended to have slightly higher serum insulin levels compared to non-myopes (75.77±2.83 vs. 70.19±2.24 pmol/L), however this difference was not significant (p=0.14), while no significant difference in the serum glucose levels of these two groups was found (5.23±0.38 vs. 5.20±0.03 mmol/L, p=0.52). Neither serum glucose nor insulin levels proved to be significantly correlated with SER in this population (Figure 2.3c-d, both R^2 ≤ 0.0001, p≥0.73).

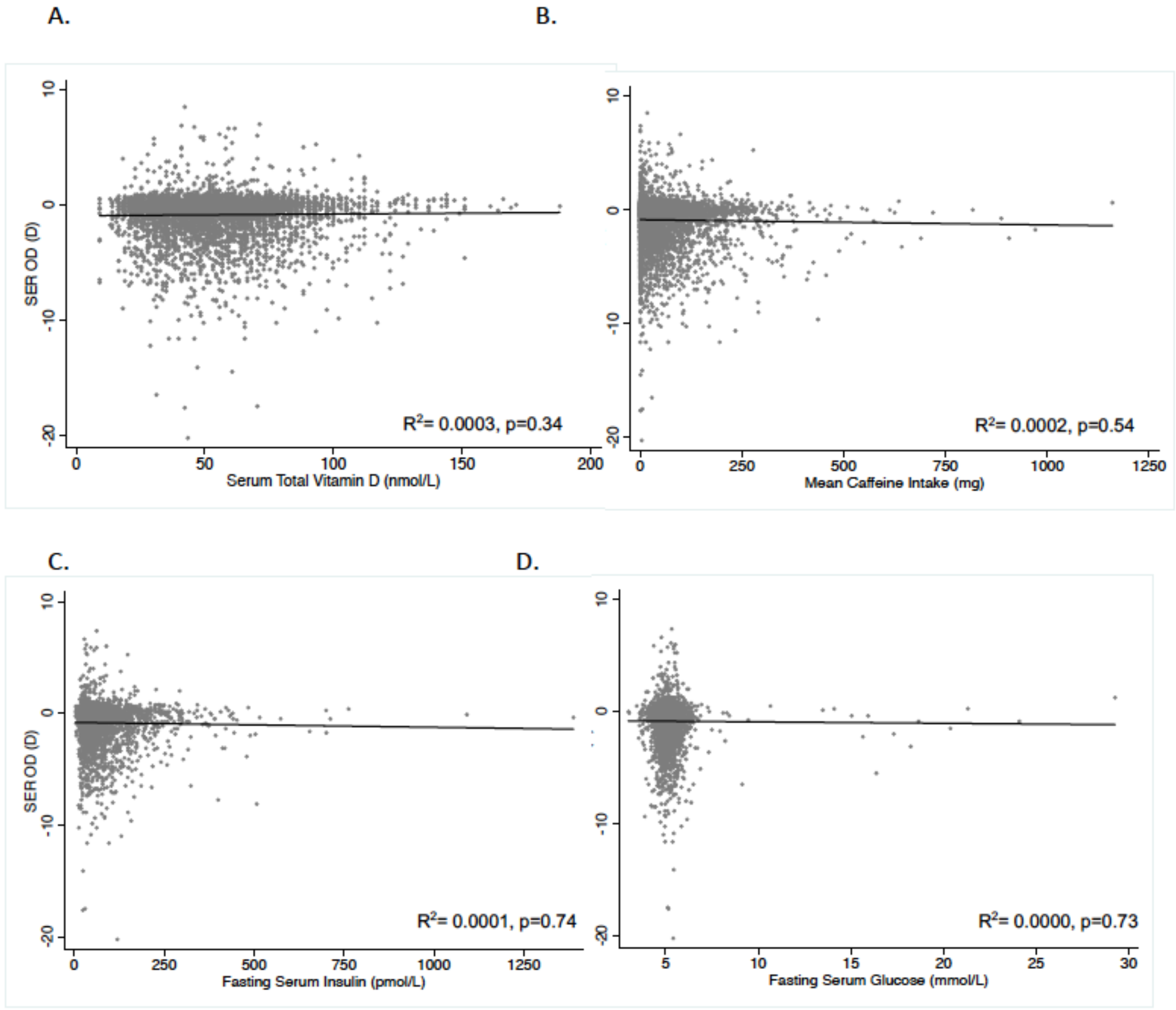

Figure 2.3: Nutritional Factors and Refractive Error. Relationship between serum Vitamin D level (A), caffeine (B), fasting serum glucose level (C) and fasting serum insulin level (D) and spherical equivalent refractive error (D) of right eyes. There was no significant correlation amongst any of the nutritional factors and SER in the study population.

Table 2.2: Summary statistics (mean±se) for body metric and nutritional factors derived for weighted population.

		ETHNICITY					REFRACTIVE ERROR STATUS	
Factors (mean±se)		**White**	**Black**	**Mex. Am.**	**Other Hisp.**	**Multi/ Other**	**Myope**	**Non-myope**
Standing Height (cm) $^{\# \wedge}$	*Male*	174.65±0.32	173.83±0.43	168.47±0.26	168.97±0.77	169.45±1.09	174.03±0.38	172.84±0.27
	Female	163.40±0.18	162.32±0.27	158.36±0.27	158.86±0.71	159.65±0.77	162.54±0.23	162.00±0.19
BMI (kg/cm^2)	*Male*	24.51±0.20	25.26±0.33	25.48±0.32	24.99±0.54	23.48±0.65	25.24±0.28	24.42±0.17
	Female	24.55±0.27	27.36±0.30	25.51±0.28	25.35±0.71	22.36±0.59	24.54±0.28	25.27±0.26
Vitamin D(mmol)$^{\wedge}$	*Male*	68.78±1.33	41.47±1.17	55.20±1.80	55.62±2.25	51.51±3.41	60.90±1.53	62.54±1.35
	Female	73.69±2.05	39.14±1.12	51.00±1.32	56.67±2.46	47.34±2.87	63.05±1.64	64.00±2.05
Caffeine (mg) $^{\# \wedge}$	*Male*	91.48±3.85	34.23±3.02	57.61±3.02	53.38±5.55	78.00±20.11	76.61±5.95	77.63±3.24
	Female	71.71±3.80	34.37±3.06	43.30±2.91	52.95±8.87	49.11±8.11	63.12±3.28	59.30±2.97
Glucose (nmol/L) $^{\# \wedge}$	*Male*	5.35±0.05	5.22±0.07	5.46±0.07	5.31±0.05	5.36±0.07	5.40±0.07	5.32±0.04
	Female	5.01±0.03	4.92±0.03	5.18±0.06	5.29±0.24	5.04±0.05	5.04±0.04	5.03±0.03
Insulin (pmol/L)$^{\wedge}$	*Male*	67.38±3.54	71.09±3.60	75.29±3.94	79.02±6.93	59.22±7.05	72.44±3.92	67.19±3.21
	Female	70.03±3.22	96.09±5.54	87.62±3.69	78.98±8.70	61.42±6.03	79.09±3.93	73.99±2.69

\# = significant difference between males and females (data pooled across ethnicity & refractive error status)
^ = significant difference across ethnicity (note Vitamin D borderline (p=0.01))
Note: no significant differences found related to refractive error status for any nutritional factor

Multi-Variable Modeling

Results for all weighted multivariate models are summarized in Table 2.3. An initial weighted linear regression multivariate model was created to identify the factors associated with participant refractive error, i.e. SER. While no significant associations between any of the demographic, body metric or nutritional factors and participant *SER* were identified, the relationships between age and female sex and a more myopic refraction, both reached/approached statistical significance (-0.05 D more myopia per 1 year increase in age, p=0.01; females more myopic by -0.34 D, p=0.026). In addition, Mexican American participants were relatively more hyperopic compared to Whites (by 0.24 D), although this difference was of borderline significance (p=0.051).

In relation to whether or not a participant had myopia, the odds [95% CI] were slightly greater for females than males (OR=1.36 [0.96 – 1.92]), with this difference approaching statistical significance (p=0.08). However, none of the other demographic, body metric or nutritional factors, proved to have predictive value, neither did age.

Additional linear regression modelling was undertaken using the data from those participants who were both myopic and had all other variables measured (n=755), with specific interest in associations between the demographic, body metric and nutritional factors and magnitude *of myopia* (data not shown). While female myopes had more myopic SERs than male myopes on average (by -0.38 D), this difference was not statistically significant (p=0.086). Older myopic participants also tended to be more myopic than younger participants, although this effect of age was neither statistically nor clinically significant (-0.06 D more per 1 year increase; p=0.15). On the other hand, there is a hint of ethnicity-related differences; specifically myopes in the Other Hispanics group were more likely to be more myopic (lower SERs, by 0.70 D), compared to Whites (p=0.02). None of the body metric and nutritional factors proved to have predictive value, as determinants of the magnitude of myopia (all p-values > 0.20).

Table 2.3: Results generated from weighted multivariate models, with adjustment for demographic, nutritional and body metric factors.

	Mean Refractive Error		**Presence of Myopia**	
	Coefficient [95% CI]	*p-value*	*Odds Ratio [95% CI]*	*p-value*
Female	-0.33 D [-0.61 to -0.04]	0.03*	1.36 [0.96 to 1.92]	0.20
Age (1-yr increase)	-0.05 D [-0.09 to -0.01]	0.01*	1.03 [0.98 to 1.08]	0.08
Ethnicity				
Non-Hispanic White	*Reference*		*Reference*	
Non-Hispanic Black	0.06 D [-0.24 to 0.36]	0.68	1.02 [0.68 to 1.53]	0.93
Mexican American	0.24 D [0.00 to 0.47]	0.05	0.77 [0.53 to 1.12]	0.17
Other Hispanic	0.15 D [-0.48 to 0.78]	0.63	1.12 [0.40 to 3.13]	0.83
Multi / Other	-0.29 D [-1.06 to 0.48]	0.45	1.18 [0.56 to 2.47]	0.65
Vitamin D	0.003 D [-0.003 to 0.009]	0.29	1.00 [0.99 to 1.01]	0.68
Caffeine Intake	0.0003 D [-0.001 to 0.001]	0.53	1.00 [0.998 to 1.001]	0.89
Glucose	-0.12 D [-0.316 to 0.083]	0.24	1.13 [0.002 to 1.75]	0.33
Insulin	-0.0002 D [-0.002 to 0.002]	0.82	1.00 [0.998 to 1.00]	0.79
Body Height	-0.002 D [-0.016 to 0.011]	0.72	1.01 [0.99 to 1.03]	0.32
Body Mass Index	0.02 D [-0.006 to 0.043]	0.13	0.99 [0.95 to 1.02]	0.41

* approached statistical significance

DISCUSSION

The study reported here represents only the second one to exploit the NHANES database as a resource for investigating environmental contributions to the develpoment of myopia. As noted in the methods, the data were weighted to adjust for ethnicity differences between the sampled population and the US population at large. After weighting, the prevalence of myopia in the 12-25 years cohort used in this study was slightly higher in females (39%) than in males (33%), and its prevalence also tended to lower in Hispanic and Mexican American group compared to Whites. However, overall, ethnicity was not signicantly associated with either the presence of myopia or its magnitude. More myopic refractive errors were also more likely to occur in females and older participants. However, neither of the body metrics studied, i.e. body mass index and standing height, proved to be associated with the presence or magnitude of myopia. With respect to the nutritional factors examined, low serum Vitamin D levels do not appear related, even at a minimal level, to the prevalence of myopia, and likewise, the glucose, insulin and caffeine nutritional metrics do not appear to be related to myopia in this population.

In relation to previous studies reporting the *prevalence* of myopia in the US, one did make use of a large NHANES cohort, involving the period 1999-2004, by Vitale et al. (2009). That study reported a slightly larger myopia prevalence figure than that reported here (42 vs. 34%). Possible explanations for the discrepancy include the narrower age range of the cohort and the reliance on objective refractive error measures used in our study. Nonetheless, consistent with the findings reported here, females have consistently been reported to have a higher prevalence of myopia and to be more myopic in past studies, including that of Vitale et al. (Czepita et al., 2007; Hyman et al., 2005; Vitale et al., 2009). Regarding ethnicity, high myopia prevalence figures and rates of myopia progression are a consistent finding for Asian ethnic groups, regardless of country of residence, in recent studies (Hyman et al., 2005; Logan et al., 2011; Pan et al., 2012; Rudnicka et al., 2010; Saw et al., 2014). In the current study, the fact that the small Other/Mixed ethnic category recorded the highest prevalence (47%, 12% more than average) and magnitude of myopia (-3.13 D; 0.46 D more than the population average), likely reflects the fact that Asian participants were included in this ethnic category, although this effect of ethnicity proved not to be significant after controlling for other participant characteristics.

The influence of *body metrics* has been previously evaluated in the context of myopia development and progression, with a number of population-based studies across the globe reporting relationships between increased eye length and/or myopia in taller individuals (Bikbov et al., 2019; Eysteinsson et al., 2005; Huang et al., 2014; Saw et al., 2002; Wang et al., 2011; Wu et al., 2007; Yin et al., 2012; Zhang et al., 2011). Note that these studies have generally involved older cohorts (≥40 years of age), with likely stable refractive errors, except for two Asian studies, which observed children aged 7-9 years of age(Huang et al., 2014; Saw et al., 2002). Interestingly, in one such population-based study of Chinese adults (Wong et al., 2001) and another of Taiwanese children (Huang et al., 2014), height was found to be positively associated with longer eyes, but not with myopia, the likely explanation lying in the other structural differences found in the eyes of taller individuals, namely deeper anterior chambers, thinner lenses, and flatter corneas. The latter findings are generally consistent with those of a systematic review of ocular biometry data, which found men to have longer eyes (by ~0.50 mm), flatter corneas (by ~0.50 D) and deeper anterior chamber depths (by ~0.16 mm) compared to women, except for those of Asian ethnicity who had steeper corneas than females (Hoffer and Savini, 2017). These results are also consistent with the common clinical observation that while males tend to have longer eyes, they also tend to be taller and are less likely to be myopic. One of the few exceptions in relation to studies of body metrics in the context of myopia is one large Israeli cohort study of conscripted males aged 17-19 years, which did not find any relationship between myopia and either body height or mass index (Rosner et al., 1995).

As noted in the introduction, *glucose and insulin* attracted the attention of Cordain et al. who proposed a hypothesis linking to hyperinsulinemia with myopia development (Cordain et al., 2002), and other studies have reported links between diabetics and myopia (Fledelius, 1986; Sjolie and Goldschmidt, 1985). However, that lenticular changes offer an explanation for the increased prevalence in myopia in the latter group is supported by results from a later small study by some of the same researchers (Goldschmidt and Jacobsen, 2014). Nonetheless, that the glycemic profiles of populations worldwide might explain observed increases in myopia prevalence figures was suggested by the authors of a recent review of related epidemiological literature, which included speculation on possible mechanisms whereby insulin could promote ocular growth (Galvis et al., 2016). Support of this theory from studies involving animal models is equivocal; while insulin was found to promote myopia development a few studies involving chicks, its effect was limited to the anterior segment and choroid (Feldkaemper et al., 2009; Zhu and Wallman, 2009).

Because serum levels of Vitamin D are known to be tightly tied to time spent outdoors (for a review see Pan et al., 2017), which is recognized to be protective against myopia, there has been interest in whether increasing Vitamin D levels alone might be protective. A number of related hypotheses concerning how low serum Vitamin D levels could increase the risk of myopia have been proposed, including: 1) up-regulation of scleral extracellular remodeling, and 2) synergistic interaction with retinoic acid, a recognized ocular growth regulator (for more detailed reviews, see Ramamurthy (Ramamurthy et al., 2015) and Pan (Pan et al., 2017)). However, consistent with results of the current analyses, three large cohort studies reported little to no effect, with respect to a low level of Vitamin D being a risk factor for the development of myopia(Choi et al., 2014; Guggenheim et al., 2014; Tideman et al., 2016). Furthermore, in the current study, Blacks had the lowest serum levels of Vitamin D, as has been reported in previous studies (Harris, 2006), yet Blacks also had the lowest prevalence of myopia of the current cohort (35%, 1% below the average), with similar findings contained in other reports (Hashemi et al., 2018; Hyman et al., 2005; Vitale et al., 2009). To-date, four randomized control trials (RCTs) investigating the effect of increased outdoor activity have been completed, all in East Asia (China and Taiwan), where the myopia problem is most severe (He et al., 2015; Jin et al., 2015; Wu et al., 2013, 2018), with varied treatment effects (Figure 1.4). While it is not possible to disentangle any potential direct role of *Vitamin D* level in the protective effects reported therein, the accumulating evidence summarized here would argue against this possibility. Also consistent with this concluion is one study in tree shrews where Vitamin D3 supplementation did not alter the development of experimentally-induced myopia (Siegwart et al., 2011). The results presented here also do not shed any new light on the possible relationship between outdoor activity and myopia, because only a small subset of 20-40 year-old NHANES participants (15.3% of our participant cohort) completed two relevant questions concerning sunlight exposure ((1) how often you stay in the shade and (2) how often use a wide-brimmed hat). Answers to these questions were part of a dermatology database and were not available for all of the 6 years targeted (i.e. 2003-2008) in the analyses reported here. Despite this, we performed a sub-population analysis to determine if there was any modification of the null relationship between Vitamin D and refractive error after consideration of outdoor activity. The responses were quite skewed, with 67% of the surveyed population reporting that they at least ‘sometimes’ stay in the shade and conversely, 63% stating that they ‘never’ wore a wide-brimmed hat that shaded their head and neck. There was no apparent difference in the proportion of each response by sex, gender, ethnicity, or presence of myopia (data not shown).

As noted in the introduction, a number of animal model studies have yielded strong supporting data for the potential therepeutic (antimyopia) benefits of caeffine and one of its metabolite, 7-methylxanthine (7-MX), a non-selective adenosine receptor antagonist(Hung et al., 2018a; Nie et al., 2012; Trier et al., 1999). Results of a pediatric clinical trial of oral 7-MX in Denmark also yielded promising results, with reduced axial elongation and myopia progression compared to the placebo group, although myopia progressed once the treatment was terminated (Trier et al., 2008). Longer-term clinical trials are on-going in Denmark, the only country to have approved oral 7-MX tablets for myopia control to-date. Unfortunately, the analyses reported here were limited to NHANES survey-based data, as analysis of urine samples for caffeine metabolites only began in 2009 (when refractive measures were discontinued).

To date, there has been no systematic analysis of this open-access NHANES dataset with respect to myopia development and/or progression and nutritional factors. The large ethnically-diverse NHANES participant cohort combined with the weighted analyses used in the current study represent its major strength, with the availability of objective and reliable refractive error data representing an additional strength, given that axial length data were not available. In addition, all measurements were performed in a standardized way by trained technicians, according to well defined protocols, across all NHANES sites, adds further value to this dataset. Nonetheless, there are several limitations to consider, the most significant of which relates to the ethnic categories utilized during the study years analyzed. Given the high prevalence of myopia in Asian populations, both in Asian countries and in the US, the lack of an ‘Asian’ category represents a major limitation to the current analyses. In addition, because refractive error data were captured only for those children ≥12 years of age, when myopia would have first appeared much earlier for many of them, our ability to detect those factors contributing to the onset as opposed to the progression of myopia may have been reduced. Outdoor activity is an unresolved confounder in these analyses aimed at understanding the relationship between Vitamin D and myopia, as no comprehensive measures of outdoor activity were available in this dataset, and only minimal data concerning sunlight exposure existed, as described above.

CONCLUSION AND CLINICAL RELEVANCE

The risk factors related to myopia development and/or progression remain to be identifed and very likely there are multiple factors involved. However, clinicians are frequently called on to make recommendations about behavior modifications that might reduce myopia development and progression. While inherent factors such as sex appear to be related to the development and magnitude of myopia, based on the results of analyses reported here, neither nutritional factors such as reflected in serum Vitamin D, glucose and insulin levels, and caffeine intake, nor body metrics such as height and body mass index, appear to play roles. The results of the current analyses help to inform clinical decision-making concerning the potential risk factors for the development and/or progression of myopia.

3. Outdoor Behaviors and Myopia: An Objective Approach

INTRODUCTION

Significant recent attention has been paid to the apparent protective effect of increased outdoor exposure against myopia development and progression (for a review see (Xiong et al., 2017) and Chapter 1). However, what feature(s) of being outdoors are responsible remain to be determined, with potential contributions from the differences in lighting characteristics and/or visual experience when outdoors compared to indoors. High light intensity exposure as encountered outdoors has been the focus of most attention as a possible protective factor by a number of recent studies (Cui et al., 2013; Norton and Siegwart, 2013; Read et al., 2014), but without clear consensus. To-date, four randomized control trials investigating the effect of increased outdoor activity (e.g. more school recess time) have been completed, all in East Asia (China and Taiwan), where the myopia problem is most severe (He et al., 2015; Jin et al., 2015; Wu et al., 2013, 2018); reported treatment effects varied across studies, but were generally mild, with no clear indication that bright light is a responsible factor (Wu et al., 2018).

A significant deficiency in studies attempting to quantify the visual environment has been the reliance on subjective reports captured through questionnaires, which are well recognized to be inaccurate (Alvarez and Wildsoet, 2013; Ostrin et al., 2018) and limited in their ability to capture potentially critical details, such as the temporal pattern of exposure (dosing), which has proven influential in animal studies (Backhouse et al., 2013; Lan et al., 2014; Nickla et al., 2017). Moreover, studies using subjective reports further complicate matters by using different criteria to define outdoor exposure; for example, some studies group sports and time spent outdoors into one category (Dirani et al., 2009), some distinguish between leisure outdoor activities and sporting activities (Jones et al., 2007), and some also distinguish between weekends and weekdays (Guggenheim et al., 2014), making it difficult to compare findings across studies. These deficiencies may be the reason why, to-date, there has been no strong risk or protection factors identified for myopia development or progression, as reviewed in Chapter 1. Given advances in electronic technologies, the opportunity to collect human behavior data in a more reliable, objective and comprehensive way presents itself, with the potential to reveal yet un-discovered aspects of the visual environment and/or human behaviors, not captured in questionnaires.

Towards constructing a more detailed picture of outdoor exposure, some researchers have turned to objective measures, making use of light meters (Alvarez and Wildsoet, 2013; Dharani et al., 2012; Ostrin et al., 2018; Read et al., 2014) and/or accelerometers (Guggenheim et al., 2012; Read et al., 2014) in conjunction with traditional questionnaires. In support of this approach, a recent systematic review (Wang et al., 2018) made a call for more standardized objective measurement of outdoor activity in human myopia studies. However, those research groups employing technologies to investigate outdoor activity in children (Ostrin et al., 2018; Read et al., 2015) have not capitalized on the power of such technologies to capture the dynamic aspects of outdoor behavior. For example, the dosing (e.g., episodic rather than cumulative daily metrics) of outdoor and indoor activities in humans has received no attention from other groups to our knowledge, yet it may be important in modulating ocular growth (Chakraborty et al., 2018; Nickla et al., 2017; Phillips, 2011). As a potential biomarker for the eye's response to ocular growth factors, choroidal thickness has been shown to be modulated by bright light in chicks, at least transiently (Lan et al., 2013), and by defocus in both animal models (Troilo et al., 2000; Wallman et al., 1995; Winawer and Wallman, 2002) and humans (Chakraborty, Ranjay, Read, Scott, Collins, 2013; Chakraborty et al., 2012; Chiang et al., 2018; Wang et al., 2016). This study aimed to characterize habitual outdoor activities, including lighting characteristics, in a comprehensive, dynamic and objective manner to determine if outdoor activity is related to the presence and/or magnitude of myopia in young adults.

METHODS

Young adults (undergraduate and graduate students on the UC Berkeley campus) were recruited to participate in the study. Limited exclusion criteria included no previous history of myopia control, eye disease or eye surgery. To investigate the possible differences in outdoor activities during an academic and non-academic period, participants were asked to participate in a measurement session during each of these periods, separated by approximately 4-6 months. This timing further allowed us to investigate behaviors that might be related to any myopia progression observed in the participants. Each session involved two visits (details provided below), separated by a two-week observation period when participants were asked to wear a light-sensing device (Respironics Actiwatch Spectrum Pro). The device continuously measures overall photopic illuminance (lux), including the spectral composition of light in terms of irradiance (RGB, $\mu W/cm^2$) (spectral sensitivities; R: 600-700 nm, G: 500-600 nm B:400-500 nm) and has a built-in accelerometer that measures participant activity (counts per min (cpm)) and sleep/wake periods. The Actiwatch has been shown to be reliable in measuring sleep patterns (Mantua et al., 2016), physical activity in young adults (Lee and Tse, 2019; Puyau et al., 2004), ambient illuminance (Markvart et al., 2015) and has good between-device correlation of illuminance measures (Ulaganathan et al., 2017). The characterization of the Actiwatch's performance in illuminance measurement has been described elsewhere (Coughlin, 2008). Participants were instructed to wear this commercial light sensor and accelerometer wristwatch device on their non-dominant wrist, over clothes for 24 hours a day (except during prolonged swimming) for a 14-day period (including two weekend periods). A built-in off-wrist monitor (watch beeps when not worn) promoted participant adherence to the watch-wearing schedule. All outputs from the device represent averages over 1-minute epochs, which has been shown to provide better estimates of ambient illuminance (Ulaganathan et al., 2017).

Ocular data collected at each visit included spherical equivalent refractive errors measured under cycloplegia (30 minutes following 2 drops 1% tropicamide), with an open-field auto-refractor (Grand Seiko WR-5100K) and axial lengths (IOL Master, Zeiss). Myopia was defined as worse than -0.50 D in the right eye. Choroidal thickness was measured at seven locations (sub-foveal and 750, 1500 and 2250 μm nasal and temporal to the fovea) surrounding the foveal zone (SD-OCT Cirrus, 9 mm HD line scan centered on the fovea) was also measured. Optimal image quality was ensured during both the scan acquisition process (image quality score of at least 7/10) and the segmentation protocol. A custom automated segmentation algorithm (Matlab, (Alonso-Caneiro et al., 2013)) was utilized to identify the RPE-choroid and choroid-sclera boundary and corrected as necessary by a trained clinician. To control for lateral magnification effects, participant axial length was considered in determining the location positions for each scan. The average choroidal thickness (ChT) from a 10 μm area (approximately 3 samples) was determined at each of the locations. Data from the right eye of participants were used for all data analysis, except in two cases due to the poor quality of captured OCT images from right eyes.

Outdoor Activity Analysis

Light intensity consistent with outdoors (≥1000 lux) was used as a proxy for outdoor activity (Ostrin et al., 2018; Read et al., 2015, 2014), with all related analyses performed using custom Matlab software. Several other factors were also considered in defining an interval of 'outdoor activity': 1) outdoor activity could only occur during waking hours (as determined by accelerometer data), 2) outdoor activity for a given day could only occur between regional sunrise and sunset hours (as determined daily by Lawrence Laboratories, UC Berkeley), and 3) small spikes in illuminance (>1000 lux) were not classified as outdoor intervals and likewise, short, small dips (<1000 lux) in ambient illuminance were ignored in calculating outdoor intervals. Unique to previous studies, three outdoor exposure dosing parameters were calculated, including the time of day (hh:mm) the interval occurred, the number of intervals per day (frequency), and the length of each interval duration (e.g. dwell time, mins). Data were excluded if there were indications that the watch was not worn or covered by clothing. For each participant, the daily average and variation in episode frequency and duration were calculated in terms of means and standard deviations, for comparison across participants, considering myopia status (presence and magnitude), and across academic periods.

For analysis of the lighting characteristics, the average (mean) and variation (SD) in brightness (illuminance, lux), experienced both within an interval (for a given day) and across a day (daily average across two weeks) were computed. The spectral composition of the lighting experienced was analyzed in a similar manner, calculated as the ratio of long:short wavelength (R:B) irradiances. Given the spectral composition of light changes across the day (greater contribution of longer wavelengths in the evening) (Santhi et al., 2012; Thorne et al., 2009), we also calculated the average daily frequency of outdoor intervals occurring before versus after 12 pm for each participant.

Finally, for comparative purposes, a subjective questionnaire was administered to a subset of participants. The questionnaire inquired about daily outdoor activities during an academic period and was different from those that have been traditionally used in past studies in that it 1) was administered two times, separated by 1 week, with separate questionnaires completed to cover weekday and weekend activities in each case, and 2) only inquired about activities over the previous week or weekend. For both weekdays and weekends, the average of the two related reports provided by each participant was calculated and a weighted mean daily activity value (in minutes) was calculated for use in data analyses.

Statistical Analysis

Outdoor metric data (dosing, lighting characteristics) were graphically analyzed with respect to ocular metrics (axial length, SER, choroidal thickness) and academic period to investigate possible relationships. Summary statistics are reported in terms of mean+/-SD, unless otherwise noted. Either unpaired or paired t-tests were applied, as appropriate, unless otherwise noted, using Excel software with the data analysis tool pack.

RESULTS

Participants

A total of 55 young adult university students aged 18 to 25 years of age participated in the study. The overall demographics of the participants can be seen in Table 3.1. The participant cohort was highly un-balanced with respect to gender (85% female) but relatively balanced by myopia status (60% with myopia) and the range of myopia severity was wide (-0.625 to -8.75 D) as well as the range of axial lengths (21.83 to 27.58 mm). Of the subset of 15 participants who had data collected during both academic (AP) and non-academic (NAP) periods, only four participants were non-myopic. The time of year in which participants were observed during the study was moderately balanced by season (Spring/Summer (March-August) vs. Fall/Winter (September-February)), with 36% of the AP cohort being observed in the Spring/Summer months. Not surprisingly, those participants who were observed in both AP and NAP were well counter-balanced with respect to season (n=10 switched seasons), with n=8 participants being observed in the Fall/Winter during the AP and in the Spring/Summer during the NAP.

Given that young adult university students have been demonstrated to progress in their myopia (Kinge et al., 2000; Loman et al., 2002), we were interested in understanding what behaviors might be related to observed myopia progression over the approximately 6-month study period. However, no significant progression was observed in the 14 participants measured at both the AP and NAP study visits (range of change in SER= 0 to -0.625D), possibly reflecting the small sample size. Given this finding, no further analysis was performed with respect to the relationship between outdoor behaviors and myopia progression.

Subjective vs. Objective Measures

For a subset of 39 participants, subjective and objective measures of outdoor activity were captured during an AP. Despite being sampled over a short period of time (previous week or weekend) and repeatedly (twice over two consecutive weeks), all but three participants significantly over-reported the amount of time they spent outdoors by a considerable amount (on average difference 120 minutes, $p<0.05$, Figure 1). Although myopes and non-myopes proportionally over-estimated their outdoor activity to a similar extent (myopes: 103%, non-myopes: 108%), myopes tended to over-estimate their outdoor activity to a lesser extent compared to non-myopes, as shown in Figure 3.1 (mean (SD) over-estimation, myopes: 116 (68.3) mins, non-myopes: 145 (74.2) mins, $p=0.29$).

Table 3.1: Participant Characteristics.

Characteristic		Participants (N=55)
Gender	Male	n=8
Age (years)	Range	18-25 y
Sph. Eq. Refractive Error (D)	Mean (±SD)	-2.25 (±2.55)
	Range	2.375 to -8.75
Axial Length (mm)	Mean (±SD)	24.56 (±1.28)
	Range	21.83 to 27.96
Myopes	worse than -0.50D	n = 33
Academic Period Measured *	Academic (AP) N=49	Myopes = 31
		Non-Myopes= 18
	Nonacademic (NAP) N=21	Myopes= 13
		Non-Myopes = 8

* Note: n=11 myopes and n=4 non-myopes had measurements during both academic periods

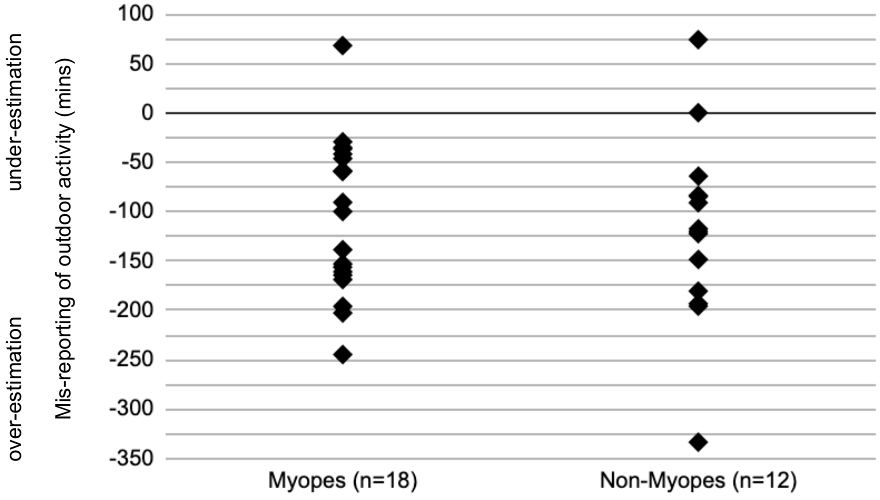

Figure 3.1: Subjective vs Objective Reports of Outdoor Activity. All but one myope (n=18) and two non-myopes (n=12) over-reported their outdoor activity on subjective questionnaires, but on average myopes over-estimated their outdoor activity to a lesser extent compared to non-myopes, (myopes: 116(68.3) mins, non-myopes: 145(74.2) mins).

Outdoor Activity Dosing

On average, outdoor activity, as measured by the Actiwatch, demonstrated that during an AP young adults go outdoors infrequently (mean (SD) count: 3.33 (1.51) intervals/day, range: 1-7 intervals/day) and for very short periods of time (mean interval duration: 10.14 (3.75) mins, range: 3-23 mins). There was minimal intra-participant variation in day-to-day behavior, as demonstrated by the standard deviation associated with daily interval count (1.88 intervals/day) and duration (5.36 mins/day). The timing of outdoor activity was biased towards afternoons for both myopic and non-myopic participants, as reflected in the higher percentage of outdoor intervals occurring in the afternoon (after 12pm) (mean (SD): myopes, 68.9 (19.3)%; non-myopes, 73.6 (14.6)%.

With respect to myopia status, there was minimal difference in the frequency of daily outdoor activity between myopes and non-myopes during the AP (mean daily interval count: myopes, 3.26 (1.49); non-myopes, 3.46 (1.58), unpaired t-test p=0.67). The mean daily outdoor interval duration was also quite short and consistent across participants, regardless of myopia status, during the AP (myopes: 9.79 (4.05) min, non-myopes: 10.74 (3.17) min, p=0.37). There was also no correlation between either the mean daily outdoor interval frequency or duration and AL or SER (Figure 3.2, $R^2 \leq$ 0.05).

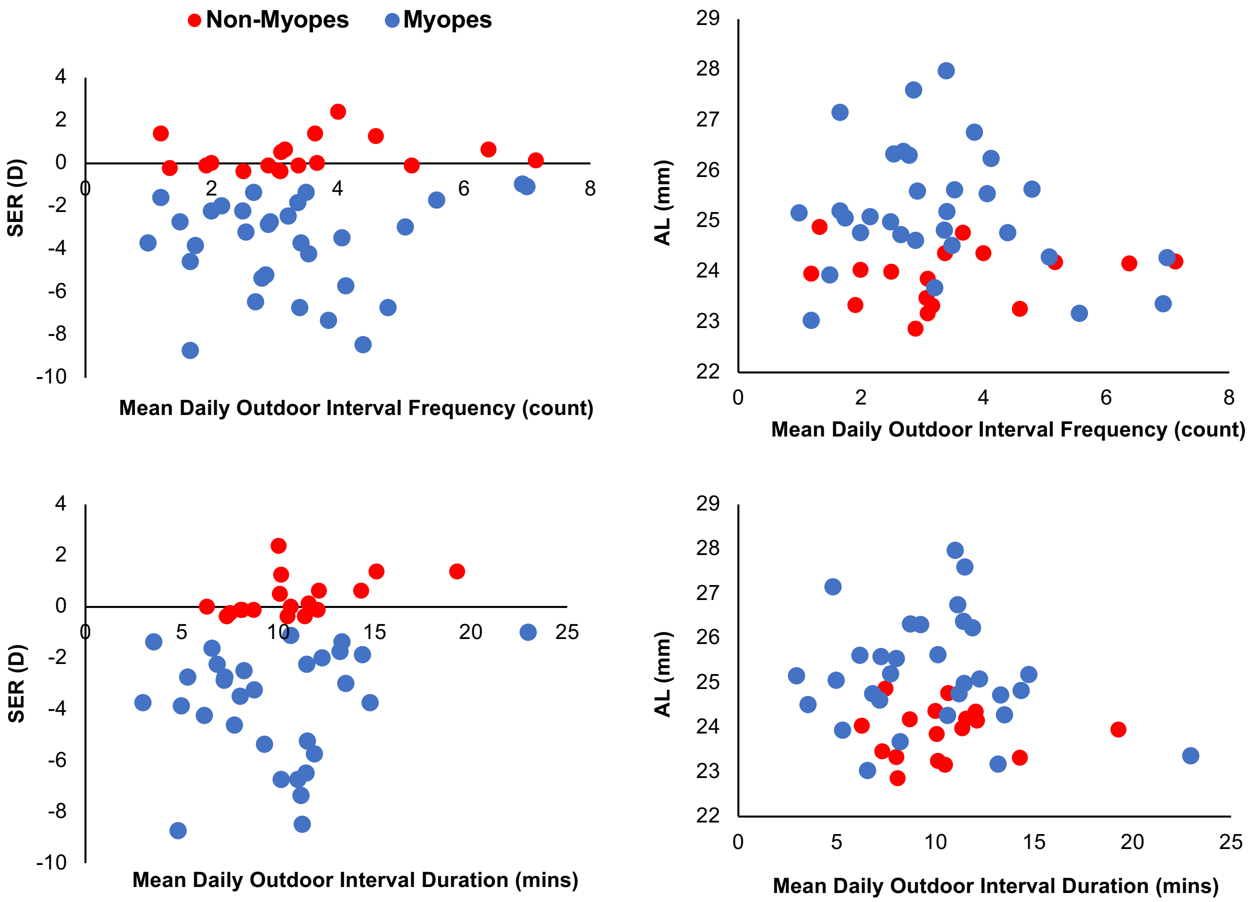

Figure 3.2: Outdoor Activity Interval Dosing in Myopes and Non-Myopes. The mean daily outdoor interval frequency (top panel) and interval duration (bottom panel) was similar in myopes (blue) and non-myopes (red) and had no significant correlation with SER (left panel) nor AL (right panel).

A comparison of the outdoor activity dosing during AP and NAP in the subset of participants for which observations were made in both periods (n=14, Figure 3.3), revealed a small but statistically significant difference in the frequency of outdoor intervals, such that all but 3 participants went outdoors more frequently in the NAP compared to the AP (by 1.2 times, on average, p=0.04). In addition, all but 4 participants went outdoors for slightly but significantly longer intervals in the NAP (by 2.56 mins more on average, p=0.04). With respect to myopia status in this limited sample, myopes demonstrated a trend towards greater modification than non-myopes in their outdoor activities in the NAP compared to the AP (Figure 3.3), going outdoors more frequently (1 interval more) and staying outdoors slightly longer (increase of 2.96 mins). The latter but not the former difference reached borderline statistical significance (p=0.42 and p=0.07, respectively).

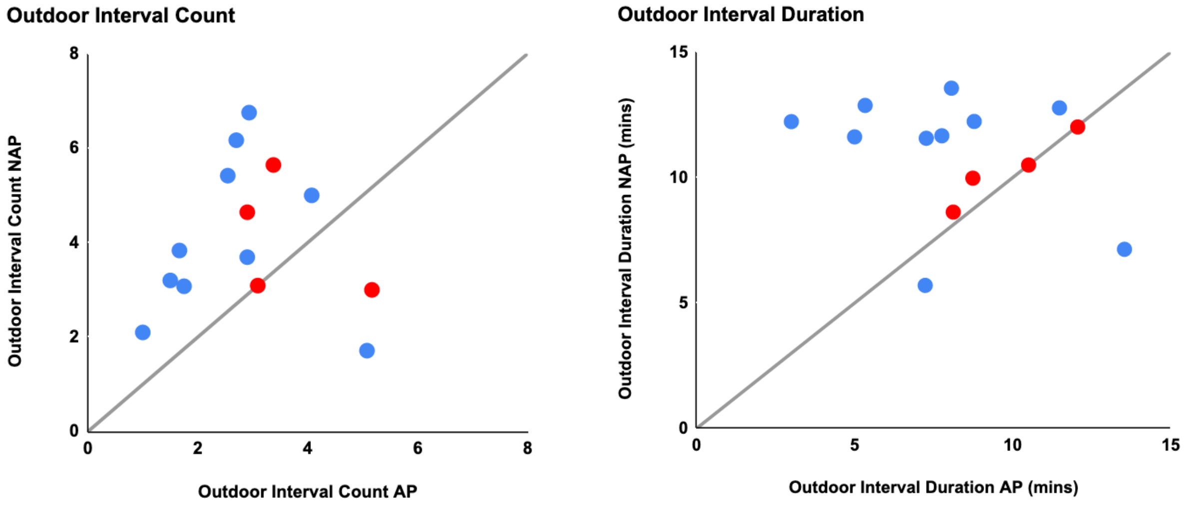

Figure 3.3: Outdoor Activity Dosing Changes with Academic Period. In participants with observations in both periods (n=14), an increase in the frequency of outdoor intervals was observed in the NAP compared to the AP (by 1.2 times, on average, $p<0.05$). Participants went outdoors for longer intervals in the NAP (2.56 mins more on average, $p<0.05$).

Outdoor Activity Lighting Characteristics

Overall, the illuminance of the outdoor environment experienced by myopes during the academic period was slightly lower compared to non-myopes (2349.66 (640.69) vs. 2554.70 (607.45) lux) although this difference was not significant (p=0.27). With respect to AL and SER, participants who experienced brighter outdoor lighting tended to have shorter eyes; however, this relationship was not statistically significant (Figure 3.4, p=0.24, $R^2 \leq 0.12$). The color of the lighting experienced when outdoors appeared to be warmer for non-myopes, as demonstrated by their higher red-light irradiance values (non-myopes:5353.68 (1987.81) μW/cm^2, myopes: 4209.78 (1763.21) μW/cm^2, p=0.05). This finding is also evident by the higher ratio of long:short wavelength (R:B) in non-myopes compared to myopes (4.92 (1.87) and 4.31 (1.58), respectively), although this difference was not statistically significant (p=0.26). This observation, however, was not apparent when comparing eye length and outdoor R:B ratio (Figure 3.4).

Finally, in those participants for whom data were collected in both academic and non-academic periods, the illuminance experienced when outdoors during each of these periods was very similar (mean difference -2.17 lux, p=0.98), although there was wide inter-participant variation, with differences between the AP and NAP ranging from 579 lux brighter to -1143 lux dimmer. There was no significant difference between myopes and non-myopes in relation to the difference of illuminance experienced between these two periods in (p=0.66). Overall, the spectral composition of the lighting experienced outdoors also showed wide inter-participant variation (R:B ratio: -4.17 to 6.26), although there was no significant difference in the R:B ratio between academic periods (mean difference (NAP-AP) =0.35, p=0.61). The difference in the R:B ratio measured across academic periods was similar in myopes and non-myopes (p=0.91).

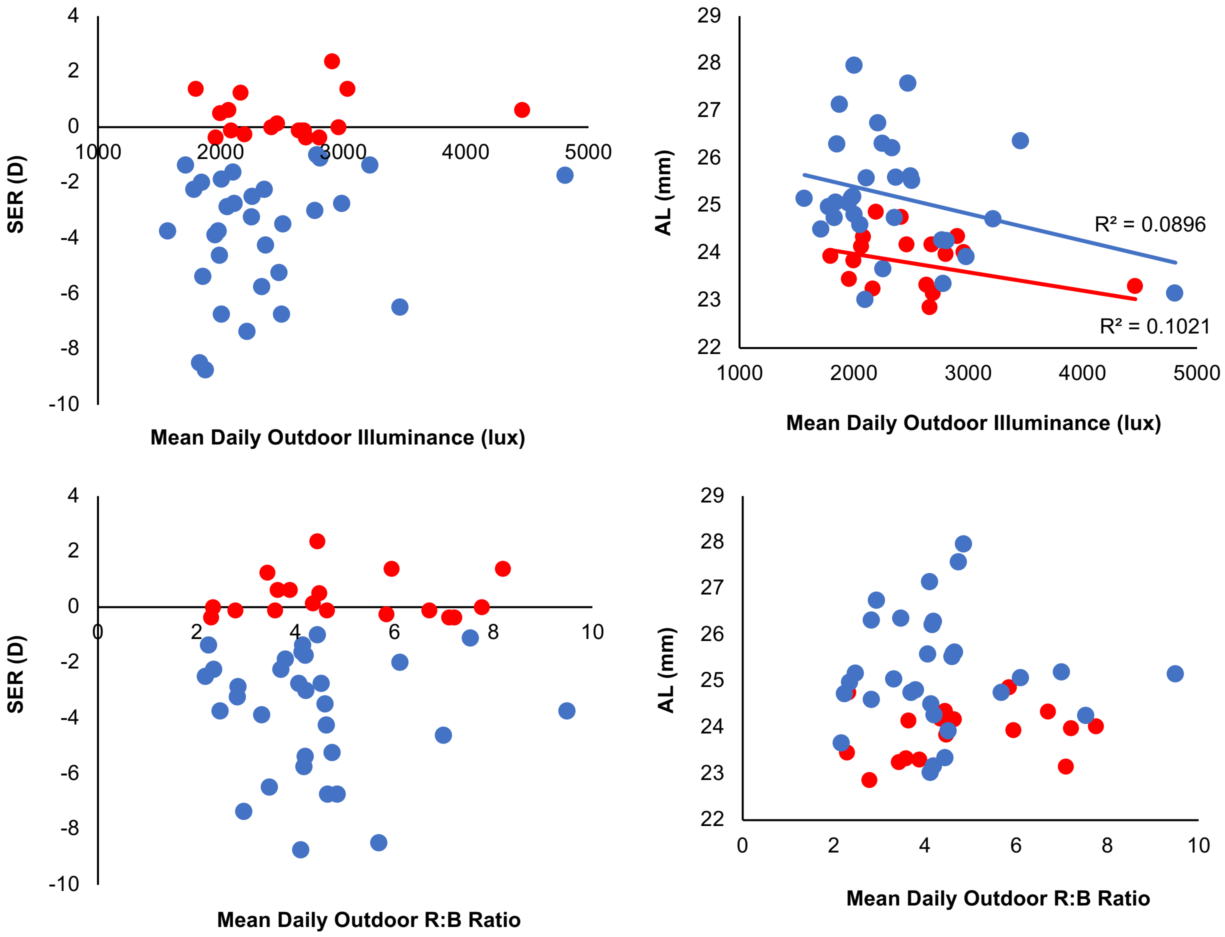

Figure 3.4: Outdoor Activity Lighting Characteristics in Myopes and Non-Myopes. The mean daily illuminance (lux, top panel) when outdoors was slightly lower amongst myopes (blue) compared to non-myopes (red). In addition, there was a mild direct correlation between outdoor illuminance levels and axial length (top-right). The spectral composition of outdoor lighting experienced, as expressed as the R:B Ratio (bottom panel) was slightly higher amongst non-myopes compared to myopes, but no significant correlation between SER or AL was observed.

Outdoor Activity and Choroidal Thickness

Choroidal thickness (ChT) data were obtained for 46 participants during the academic period. As expected, ChT was inversely correlated with axial length, with myopes tending to have thinner choroids, although there was substantial individual variability, especially in the peripheral locations (R^2 range: 0.08 to 0.18). ChT at the subfovea and 2250 μm nasal (N) and temporal (T) to the fovea was compared to outdoor behavior metrics and are shown in Figure 3.5. No relationship between ChT and outdoor interval frequency or duration was observed in myopes, however there was a trend in non-myopic participants such that those with more frequent and shorter outdoor intervals had thicker ChT (R^2 range: 0.07 to 0.14). There was no significant relationship between ChT and either outdoor lighting brightness or outdoor R:B ratio in either myopes or non-myopes (data not shown, all $R^2 < 0.06$).

The ChT at both the subfovea and the two most peripheral locations (N2250 and T2250) were also compared for participants for whom data were collected for both academic and non-academic periods. There were no significant differences in ChT across academic periods at any of the locations, regardless of participant myopia status (all p-values > 0.30, data not shown). However, there was substantial intra-participant variability in the measured ChT across the two academic periods (range of differences greater than +/- 50μm), which may reflect modulation of ChT by environmental factors that were not controlled for (e.g. caffeine, blood pressure, etc.), and/ or natural diurnal variations in ChT.

DISCUSSION

The study described here made use of an Actiwatch device, which has also been used to-date by two other groups to study outdoor behavior in the context of myopia (Ostrin et al., 2018; Read et al., 2014). However, our study is novel in that it quantified outdoor activity in a temporally more dynamic and comprehensive way than done by the other two groups. Nonetheless, there were no significant differences in the outdoor activities of myopic compared to non-myopic young university students measured in this way (i.e., interval duration and frequency), at least during an academic period. In addition, although there was a hint that exposure to increased lighting levels, as encountered outdoors, may be linked to shorter axial lengths, no significant differences between myopes and non-myopes were apparent.

In a subset of participants, we were able to compare outdoor activities during both an academic period and a non-academic period. We found small but significant increases in the frequency and duration of intervals spent outdoors in non-academic periods, with myopes apparently more likely to modify their behavior, which holds potential implications for the observation that the progression of myopia tends to be slower in the summer months during a non-academic period (Donovan et al., 2012; Fujiwara et al., 2012; Gwiazda et al., 2014).

Our preliminary results, although variable, suggest that the dynamics (e.g. dosing) of outdoor activity may be related to choroidal thickness in our small cohort of non-myopes, however we found no relationship between outdoor lighting characteristics and choroidal thickness. In relation to the variability in our results, it should be noted that the choroid has a diurnal rhythm (Nickla, 2013) and that the time of OCT imaging varied across participants. To our knowledge, only one population report has related the dosing of outdoor activity to choroidal thickness in children, in terms of the ratio of indoor to outdoor activity, and found no relationship to choroidal thickness (Zhu et al., 2017). However, some attention has been paid to the effects of lighting characteristics, including brightness and spectral composition, on the choroid in both humans (Read et al., 2018) and chickens (Hung et al., 2018b; Lan et al., 2013) and generally report that the choroid thickens in response to brighter lighting conditions. Given that the proportion of time spent indoors vs. outdoors is substantial, future work is warranted to investigate the role of indoor lighting characteristics and choroidal thickness in our participant cohort.

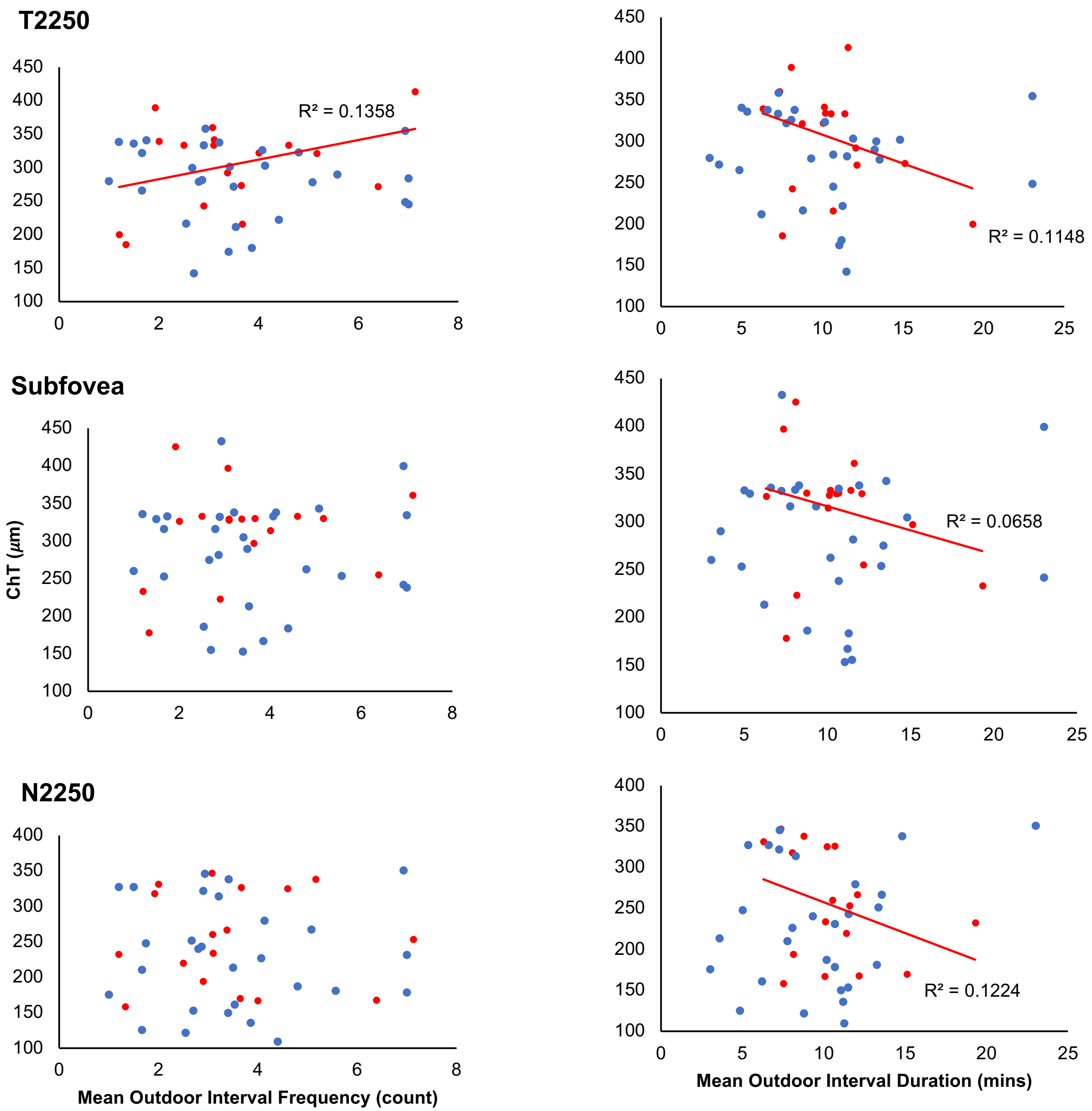

Figure 3.5: Outdoor Activity Characteristics and Choroidal Thickness. In general, mean outdoor interval frequency (left panel) was not related to ChT, except in non-myopes (red) at T2250. Longer outdoor interval durations (right panel) were related to thinner ChT in non-myopes, but not in myopes.

Interest in the role of lighting, as a potential explanation for the protective effect of outdoors, has been driven largely by results from studies using animal models of myopia in which bright light rearing conditions are reported to protect against form-deprivation myopia, for example, in monkeys (Smith et al., 2012) and in chickens (Ashby et al., 2009; Stone et al., 2016). However, the same conditions have significantly less effect on lens-induced myopia, a paradigm debated to be more relevant to the human myopia condition, in both species (Ashby and Schaeffel, 2010; Smith et al., 2013), although one study found an additive inhibitory effect of bright lighting on eye growth, when combined with myopic defocus in chickens (Zheng et al., 2018). With form deprivation myopia in chickens, the dosing characteristics (frequency of delivery and brightness) also appear to be important, with very short, frequent periods of bright lighting reported to offer better protection than continuous exposure (Lan et al., 2014), and the inhibitory effects increasing in parallel with illuminance up to 10 klux (Zheng et al., 2018). Although these studies provided the rationale for investigating outdoor dosing in humans, as undertaken here, methodological differences across these animal studies, including the brightness (and spectral composition) of the lighting used, and the dependence in most studies on form deprivation to induce myopia, make it difficult to draw conclusions from them. While the findings presented here do not clarify matters, our study does offer a new methodology to explore the dynamics of light exposure for use in future behavioral studies of myopia.

The advent of commercially available light-sensing, wearable technologies has led to an increasing number of studies, mostly involving children, in which they have been deployed to objectively measure light exposure (Cui et al., 2013; Ostrin et al., 2018; Read et al., 2015; Verkicharla et al., 2017). In general, these studies find that increased exposure to higher light levels has little to no effect on myopia progression and/or axial elongation in children (e.g., 0.07 mm or less reduction in axial elongation over 6 months to 1 year) (Cui et al., 2013; Ostrin et al., 2018; Read et al., 2015). In addition, as mentioned in the introduction, randomized control trials (RCTs) investigating the treatment effect of increased recess time spent outdoors in Asia found increased time outdoors reduced myopia incidence, by approximately 5-10%, with little to no clinically significant effect on myopia progression (or axial elongation) in already myopic children (Jin et al., 2015; Wu et al., 2013, 2018). Furthermore, in a follow-up RCT to the Taiwanese study, in which participants wore a light sensor device around their necks during the school day (Wu et al., 2018), no significant differences between the control (traditional school day) and intervention (increased recess) groups in their light exposure patterns (minutes of exposure to various light levels), either at baseline or at the end of the study, were found offering no plausible explanation for the reduced effect of the outdoor intervention.

The spectral composition of lighting has only received attention in animal studies of eye growth regulation; however, they have generally used unnatural, monochromatic conditions, which children are unlikely to encounter. To further complicate matters, there is little consistency in the results of such studies across species. For example, red and blue lighting are reported to induce myopia and hyperopia respectively in chicks (Foulds et al., 2013) and guinea pigs (Liu et al., 2011; Qian et al., 2013), while red lighting induces hyperopia in both in tree shrews and monkeys (Gawne et al. 2017, 2018, Hung et al. 2018, Smith et al. 2015). To our knowledge, to date there have been no studies that specifically investigated the potential influence of the spectral composition of lighting in human myopia development. Although we did find some evidence that outdoor lighting characteristics may be linked in young adults to myopia status or axial length, it must also be acknowledged that myopia progression tends to be slower in the population studied than in children. Thus, further investigation in children developing myopia is warranted.

There are several strengths and limitations to consider in the current study. The main strength is the use of an objective wearable technology to quantify outdoor lighting exposure and characteristics, including its spectral composition. Unlike previous published studies, which have reported cumulative outdoor exposure, i.e., sum of minutes >1000 lux recorded by the device, we quantified outdoor exposure in terms of temporal dosing parameters, that were able to capture behavioral dynamics and also avoid potential confounders such as spikes of bright indoor exposures arising from device use. Key limitations of our study relate to our participant cohort being young adults, who rarely manifest new myopia and also tend to show slower progression than children. Therefore, planned future work will investigate these behaviors dynamics in young children, for whom eye growth has not yet stabilized and both the development and progression of myopia is most prevalent. Another main limitation of our study was the significant lack of balance in our cohort with respect to gender, which is likely due to the skewed demographics of the UC Berkeley Optometry School, but may also indirectly reflect the increased prevalence of myopia observed in females (Hoffer and Savini, 2017; Roy, 2015). Other limitations include the potential confounding of our results by season of measurement across the academic and non-academic periods, the lack of control with respect to the time of day choroidal imaging took place, as well as the small number of participants who were available to participate during a non-academic period.

CONCLUSION

In conclusion, substantial mis-reporting occurs when individuals provide subjective reports of their outdoor activity as compared to objective measures. In addition, the suggestion that there is differential mis-reporting with respect to myopia status creates further concern for bias amongst the widely used traditional method of utilizing subjective questionnaires to quantify outdoor activity. In addition, although not significant in this analysis, this finding could contribute to a possible over-estimation in reports of increased time outdoors in non-myopes vs myopes. Using objective wearable technologies, several observations regarding the outdoor habits of young university students during both academic and non-academic periods have been quantified and have implications for future longitudinal pediatric studies investigating the role of outdoor activity, including lighting characteristics, on myopia development and/or progression.

4. Indoor Behaviors and Myopia: An Objective Approach

INTRODUCTION

The genesis of near work being a potential risk factor for the development of myopia stemmed from early epidemiological studies in the 19th century that hypothesized that education and excessive near work may be to blame for the incidence in myopia amongst schoolchildren and University students (Cohn, 1883; Donders and Moore, 1864). A century later, the same hypothesis was speculated to be the reason for the apparent increase in myopia prevalence amongst indigenous Eskimo populations (Young et al., 1969). Although there are several confounding variables related to other life style changes occurring around the same time as the latter observation, for example, in diet as discussed earlier, multiple factors related to near work have been targeted in related research involving both human and animal models of myopia, spanning several decades.

In relation to the amount of near work undertaken by a child, most studies have relied on subjective reports. Unfortunately, such studies have shed little light on whether the simple metric of how much a child reads is related to myopia development and/or progression. A meta-analysis of 11 studies investigating the association of hours of near work and the presence of myopia found that increased near work was associated with myopia, albeit to a small, non-clinically significant degree (summary OR:1.14) (Huang et al., 2015). In addition, the review found no effect of increased diopter-hours of near work (a metric that combines the amount and demand of near work) on future myopia development and further reported that parental reports of the habitual time spent performing various individual near work activities (reading, watching TV, studying, playing computer/video games) in myopes versus non-myopes children had no clinically meaningful differences (mean differences approx. 30 mins or less).

Two studies have reported an association between near working distances (< 30 cm) and myopia presence/severity (Hartwig et al., 2011; Ip et al., 2008), under the hypothesis that closer near working distances may increase hyperopic defocus. Consistent with the latter result, the Correction of Myopia Evaluation Trial (COMET) found that positive progressive addition lens (PAL) treatments for myopia control were more effective, albeit to a small degree, in children with habitual near working distances of less than 30 cm (Gwiazda, 2011). Together these results also support an earlier suggestion by Zylbermann et al (1993), that dynamic and closer near working distances might be related to myopia development, based on a comparison on refractive error data collected from secular and religious schools in Israel. Specifically, males in religious schools, who were required to spend significant time reading religious text while rocking back and forth in relation to the text (davening), were more likely to be myopic compared to females of similar age, who were not required to undertake the same rigorous religious studies, even when attending religious schools.

Clinicians would agree that the clinical picture of a myopic child is an avid reader who never takes gaze breaks away from their books. This anecdotal evidence may have some truth as children engaged in extended periods of near work have been shown to develop myopia earlier, and progress more rapidly (Gwiazda et al., 2004). As more direct evidence implicating gaze behavior, another study found that myopic adults took significantly fewer fixation breaks away from the ‘page’ during sustained near tasks compared to non-myopes (Harb et al., 2006). Towards any protective role of frequent gaze breaks against myopia development and/or progression, it is possible that the retinal defocus pattern experienced when viewing objects at further distances as opposed to near distances, even if only for brief periods, may also be protective against myopia (discussed further below) (Wallman and Winawer, 2004). Such gaze behavior has generally not been monitored in past studies investigating the link between near work and myopia.

While the lighting characteristics of outdoors have received a lot of attention in human myopia studies, little attention has been paid to the differences between indoor versus outdoor visual experiences, despite evidence from animal models that the nature of the optical defocus experience is critical important to eye growth (Hess et al., 2006; Smith et al., 2014). For example, imposed hyperopic defocus (retinal image behind the plane of the retina) appears to be a strong ocular growth stimulus in animals, even when limited to the retinal periphery (Benavente-Pérez et al., 2014; Liu and Wildsoet, 2011; E. L. Smith et al., 2009b). These observations have served as the foundation for both the hypothesis that accommodative lags, which produce the same hyperopic defocus, could be a risk factor for myopia. In addition, these results combined with the fact that myopic retinal defocus (image focused in front of the retina) is a strong inhibitor of eye growth (Hammond and Wildsoet, 2012; Schmid and Wildsoet, 1996; Wallman and Winawer, 2004) provides the rationale for some of the optical myopia control treatments now in use (e.g., multifocal or ortho-k contact lenses) (Kang and Swarbrick, 2011; Walline, 2016). Peripheral hyperopic defocus is likely to be more frequently encountered in crowded indoor environments, as objects nearer than the fixation distance are more likely encountered; thus indoor environments are predicted to be more myopiagenic. Attempts have been made to quantify and model the retinal defocus patterns of representative indoor and outdoor scenes (Flitcroft 2012, Charman 2011, see Figure 1.3), but no attempt to characterize the habitual visual indoor and outdoor environments of children, when myopia typically first appears and progression tends to be most rapid. Given the findings reported in an earlier chapter of this dissertation, i.e., that individuals spend substantially more time indoors than outdoors, and that the dioptric variation is much greater indoors than in outdoors, indoor environments warrant more attention in myopia research.

Therefore, the aim of the study described in this chapter was to investigate the features of habitual indoor activities, specifically the lighting characteristics and dynamics of indoor activities, as well as habitual near activity and work distance, for young university students, with and without myopia, using objective technologies, including wearable ones.

METHODS

As part of a larger project investigating the role of habitual human indoor and outdoor behaviors, the measurements and analysis presented here were performed on the same participant cohort described in Chapter 3. In brief, young adults (undergraduate and graduate students on the UC Berkeley campus) who had no previous history of myopia control, eye disease or eye surgery were recruited to participate in the study. To investigate the possible differences in indoor activities during an academic period (AP) and a non-academic period (NAP), participants were asked to come for a session during each of these periods, separated by approximately 4-6 months. Each session involved two visits (details provided below), separated by a two-week observation period during which participants were asked to wear a light-sensing device (Respironics Actiwatch Spectrum Pro). They were instructed to wear this commercial light sensor and accelerometer wristwatch device on their non-dominant wrist, over clothes for 24 hours a day (except during prolonged swimming) for a 14-day period (including two weekend periods). A built-in off-wrist monitor (watch beeps when not worn) promoted participant adherence to the watch-wearing schedule. The device continuously measures overall photopic illuminance (lux), including the spectral composition of light in terms of irradiance (RGB, μW/cm^2) (spectral sensitivities; R: 600-700 nm, G: 500-600 nm B:400-500 nm) and has a built-in accelerometer that measures participant activity (counts per min (cpm)) and sleep/wake periods. All outputs from the device represent averages over 1-minute epochs.

To quantify the near and intermediate activities of our participants two ‘objective’ methods were employed during the 2-week observation period. First, the participants were asked about the activities undertaken on a particular day, making use of a unique feature of the Actiwatch, specifically its ability to summons a participant (by beeping) to key in a numerical response (range of 1-15) to a pre-determined question(s) at a customized time(s) of day. For each participant, the watch was programmed to beep daily 1 hour prior to their habitual bedtime and the participant was instructed to key in the number of hours spent on near activities (defined as nearer than an arm’s length away, Question 1) and intermediate activities (defined as approximately an arm’s length or more away, Question 2) for that particular day. Second, participants were asked to turn on their computer’s Photobooth video-recording application during a period of time when they were planning to undertake approximately 1 hour of habitual computer work. Participants were instructed to run the program in the background by minimizing the application window. Video recordings captured by each participant were uploaded to a secure server for analysis. The habitual working distance of each participant was derived from their video recording; in total, 10 estimates were made, approximately 6 mins apart per video, from their inner canthus to inner canthus distance (or glasses bridge width for those that wore glasses), and an empirical calibration function.

Ocular biometry data collected at each visit included spherical equivalent refractive error (SER) measured under cycloplegia (30 minutes following 2 drops 1% tropicamide), with an open-field auto-refractor (Grand Seiko WR-5100K) and axial length (AL, IOL Master, Zeiss). Myopia was defined as worse than -0.50 D in the right eye. Choroidal thickness (ChT) was also measured at seven locations surrounding the foveal zone (sub-foveal and 750, 1500 and 2250 μm nasal and temporal to the fovea, SD-OCT Cirrus, 9 mm HD line scan centered on the fovea). Optimal image quality was ensured during both the scan acquisition process (image quality score of at least 7/10) and the post-imaging segmentation protocol. Specifically, a custom automated segmentation algorithm (Matlab, (Alonso-Caneiro et al., 2013)) was utilized to identify the RPE-choroid and choroid-sclera boundary and corrected as necessary by a trained clinician. To control for lateral magnification effects, participant axial length was considered in determining the seven location positions for each scan. The average ChT from a 10 μm area (approximately 3 measurements) was determined at each of the locations. Data from the right eye of participants were used for all data analysis, except in two cases due to the poor quality of captured OCT images from right eyes.

Indoor Activity Analysis

Light intensity consistent with indoors (<1000 lux) was used as a proxy for indoor activity (Ostrin et al., 2018; Read et al., 2015, 2014) and all analyses were performed using custom Matlab software. Several other factors were also considered in defining an interval of ‘indoor activity’; 1) indoor activity could only occur during waking hours (as determined by accelerometer data) and 2) attention was paid to not classify small dips in illuminance (<1000 lux) as an indoor interval and also not shorten an interval because of a small spike (≥1000 lux) in ambient illuminance. Unique to this study, two indoor exposure dosing parameters were calculated: 1) the number of intervals per day (frequency) and 2) the length of each interval duration (e.g. dwell time, mins). Data were excluded if there were indications that the watch was not worn or covered by clothing.

As described for the analysis of outdoor activity in Chapter 3, the daily average and variation in episode frequency and duration were calculated in terms of means and standard deviations for comparison across participants, considering myopia status (presence and magnitude). For analysis of the lighting characteristics, the average (mean) and variation (SD) in brightness (illuminance, lux), experienced indoors, both within an interval (for a given day) and across a day (daily average across two weeks) were computed. The spectral composition of the indoor lighting experienced was represented as the ratio of long:short wavelength (R:B) irradiances.

Near and Intermediate Activity Analysis

From the Actiwatch near and intermediate activity responses, a daily average of total combined near and intermediate work was calculated for each participant. For comparison purposes, traditional subjective questionnaires about daily near/intermediate activities during an academic period were administered to a small subset of participants. As described in Chapter 3, these questionnaires were different from those traditionally used in myopia-related studies in three important ways: 1) they were administered separately for weekday and weekend activities, 2) inquiries were limited to activities over the previous week or weekend, and 3) they were administered twice, separated by 1 week during the 2-week behavior observation period. The average of the two reports provided by each participant was calculated for both weekdays and weekends and a weighted mean daily activity value ((5 x weekday average) + (2 x weekend average)) / 7), in hours) was calculated from averaged weekday and weekend reports and used for all data analyses comparing subjective to objective measures of near work. For the sake of brevity and given that data analysis was performed on the daily average of combined near and intermediate activities, all near / intermediate activity will be referred to in the remainder of this chapter as ‘near’ activity.

Statistical Analysis

Indoor metric data (dosing, lighting characteristics, ‘near’ activity performed, habitual working distance) were graphically analyzed with respect to ocular metrics (AL, SER, ChT). ‘Near’ activity was compared across academic and non-academic periods to investigate for possible differences in behavior. Summary statistics are reported in terms of mean+/-SD. Unpaired or paired t-tests were applied to the data, unless otherwise noted, and all were computed using the Excel data analysis tool pak.

RESULTS

Participants

A total of 56 young adult university students aged 18 to 25 years of age participated in the study. The overall demographics of the participants are summarized in Table 3.1.

Indoor Activity Dosing

On average, indoor activity, as measured by the Actiwatch, demonstrated that young adults spent significant periods of time indoors during an AP (mean (SD) count: 12.12 (2.37) intervals/day, range: 6.25 to 17 intervals/day, mean interval duration: 58.31 mins, range: 25.35 to 119.77 mins). While there was minimal intra-participant variability in day-to-day behavior with respect to the number of indoor intervals per day, as demonstrated by the on-average standard deviation associated with daily interval count (3.96 intervals/day), there was more intra-participant variability in the duration of each interval (74.72 mins/interval).

With respect to myopia status, there was no significant difference in the frequency of daily indoor activity between myopes and non-myopes (mean daily interval count: myopes, 12.36 (2.10); non-myopes, 11.72 (2.79)). There was also no correlation between the mean daily frequency of indoor activity and SER or axial length (Figure 4.1, $R^2 \leq 0.06$). The mean daily interval duration was also consistent across participants, regardless of myopia status, (myopes: 57.27 (21.73) min, non-myopes: 60.09 (26.38) min) and here also, there was no relationship between mean daily indoor interval duration and SER or AL (Figure 4.1, $R^2 \leq 0.07$).

A comparison of the indoor dosing during an AP and NAP in the subset of participants for which observations were made in both periods (n=14, Figure 4.3), showed that there was no significant difference in either the interval frequency (mean NAP-AP difference: 0.37 intervals/day, p=0.62) or duration (mean NAP - AP difference: -3.26 mins/intervals, p=0.66). In addition, there was no significant difference in the interval frequency and duration changes observed across the two periods by myopia status (p=0.32 and 0.65, respectively).

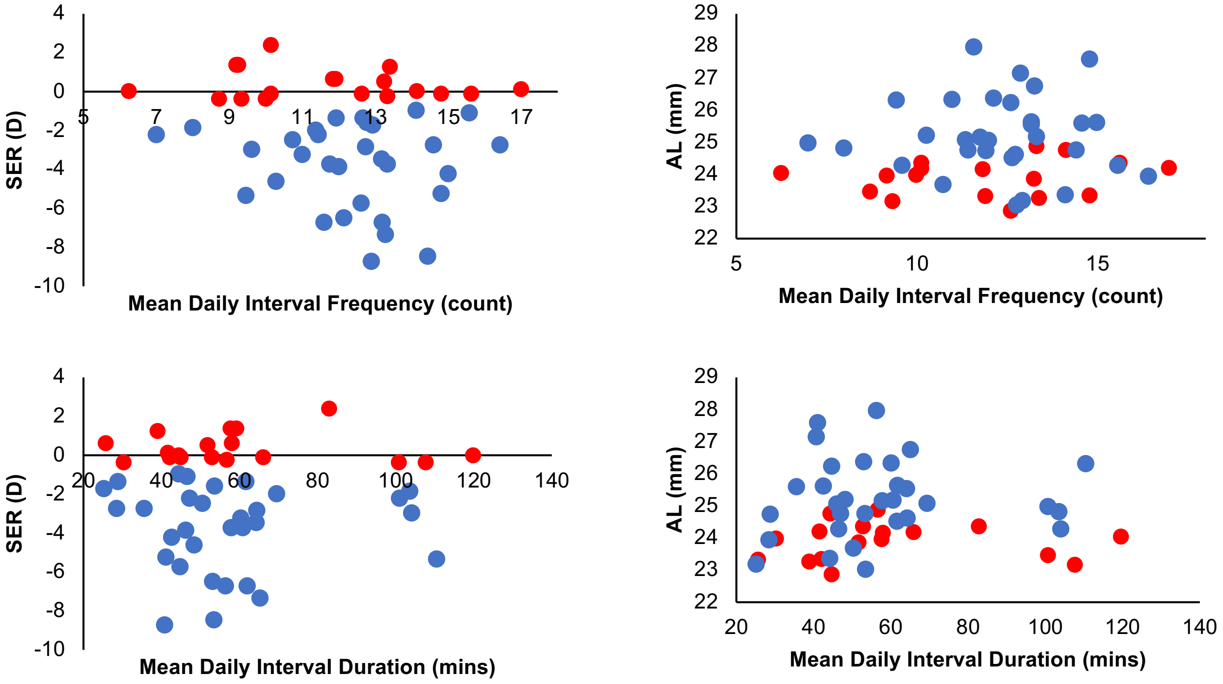

Figure 4.1: Indoor Activity Interval Dosing in Myopes and Non-Myopes. The mean daily indoor interval frequency (top panel) and interval duration (bottom panel) was similar in myopes (blue) and non-myopes (red) and had no significant correlation with SER (left panel) nor AL (right panel).

Indoor Activity Lighting Characteristics

Overall, the brightness of the indoor environment experienced by myopes during an AP was slightly brighter and more variable compared to that experienced by non-myopes (217.86 (155.90) vs. 182.60 (77.14) lux), but this difference was not significant (unpaired t-test, p=0.30). In addition, myopes tended to experience more variation in indoor illuminance within a day, as evident by the mean standard deviation in illuminance across indoor activity intervals for a given day (mean: myopes, 337.88 lux, non-myopes, 282.69 lux, p=0.45). However, there was no apparent relationship between AL or SER and indoor illuminance levels (Figure 4.2, $R^2 < 0.05$).

In general, the color of the lighting experienced when indoors as compared to outdoors, was cooler (e.g. proportionally less long wavelength light) as reflected in the reduced ratio of long:short wavelength (R:B ratio) (2.95 (0.63) and 4.54 (1.70), respectively) and the indoor experiences of, non-myopes and myopes were similar (R:B ratios: 2.99 (0.67) and 2.93 (0.61), respectively, p=0.77). Nonetheless, myopic participants who experienced proportionally more long wavelengths when indoors (higher R:B ratio) were significantly more myopic and had longer eyes (Figure 4.2, $R^2 =$ 0.14-0.15, $p \leq 0.04$).

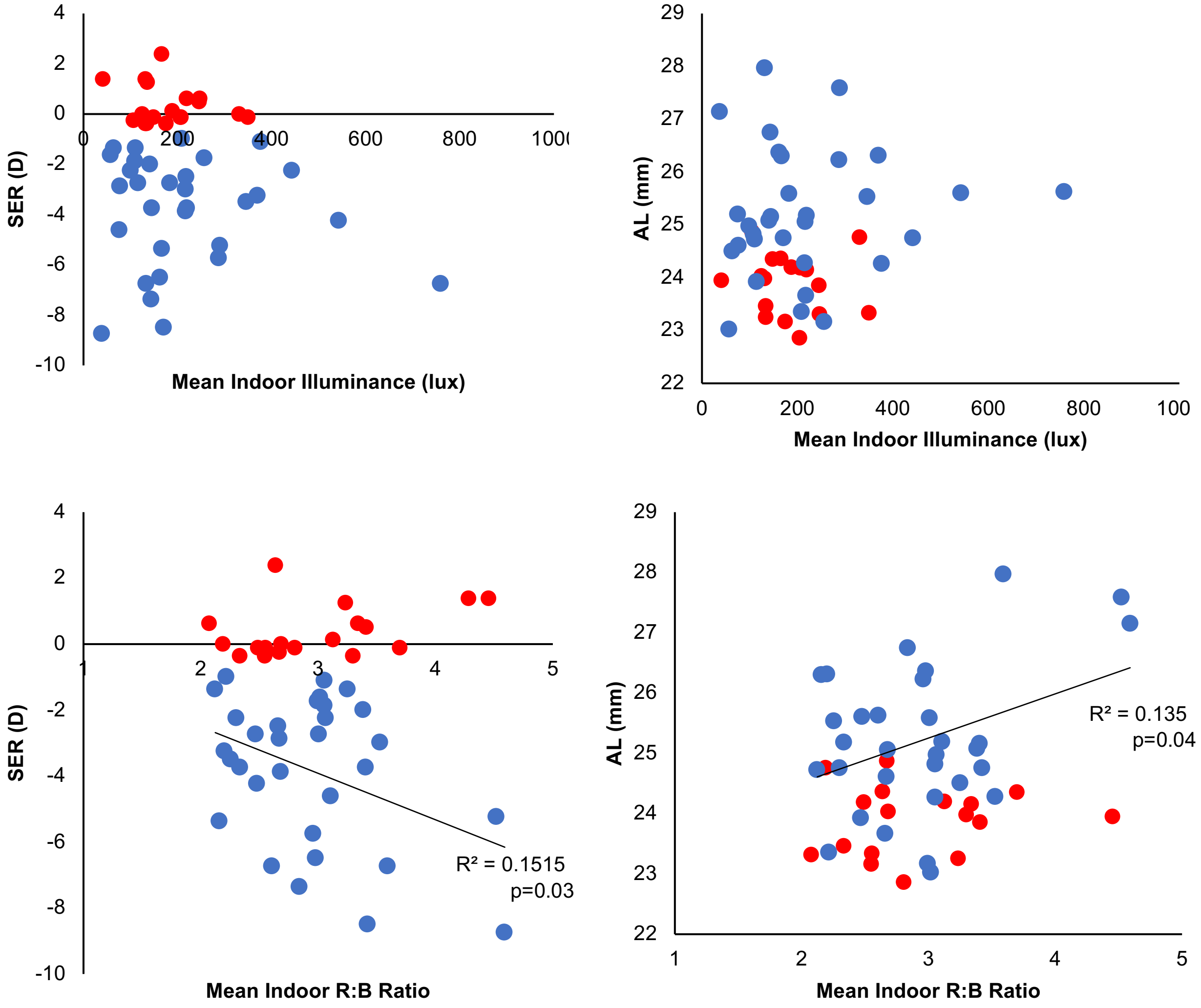

Figure 4.2: Indoor Activity Lighting Characteristics in Myopes and Non-Myopes. The mean daily illuminance (lux, top panel) when indoors was slightly higher amongst myopes (blue) compared to non-myopes (red), although there was no correlation with SER (left) or AL (right). The spectral composition of outdoor lighting experienced, as expressed as the R:B Ratio (bottom panel) was similar in non-myopes and myopes, however higher R:B Ratios was significantly related to more myopia (p=0.04) and longer eyes (p=0.03) within myopes.

Finally, for those participants for whom data were collected in both an AP and NAP, the indoor illuminance experienced during each of these period was very similar (mean difference -34.7 lux, p=0.12, Figure 4.3), although there was wide inter-participant variation, with differences in mean values for NAP and AP ranging from 103.67 lux brighter to -267.29 lux dimmer. The latter variability was not related to refractive error; the differences in mean indoor illuminance between these two periods was not significantly different between myopes and non-myopes (p=0.98).

Overall, the spectral composition of the indoor lighting experienced in a NAP vs. AP also showed wide inter-participant variation (R:B ratio: -0.99 to 2.35), although, on average, participants experienced proportionally more long wavelengths in the NAP and this difference approached statistical significance (mean difference (NAP-AP) =0.45, p=0.07, Figure 4.3). The difference in the R:B ratio across the two periods was also slightly higher in myopes compared to non-myopes (NAP-AP: 0.56 and -0.26, respectively (p=0.09), suggesting that myopes experience slightly warmer light in a NAP versus AP, compared to non-myopes.

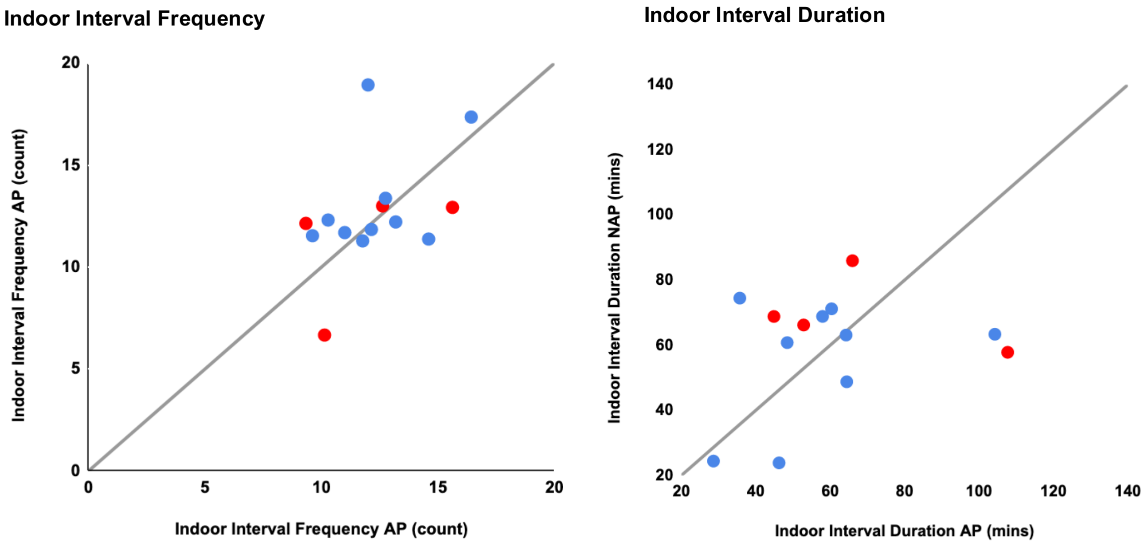

Figure 4.3: Indoor Activity Dosing is Stable with Academic Period. In participants with observations in both periods (n=14), the frequency and duration of indoor intervals was similar in NAP compared to the AP.

‘Near’ Behavior

For a small subset of 8 participants during an AP, subjective (questionnaire-based) and more ‘objective’ (Actiwatch-based) measures were captured regarding amount of daily ‘near’ activity performed. Despite sampling being limited to a recent and relatively short period of time (previous week or weekend) and repeated (twice over two consecutive weeks), there were significant disparities in the reported amount of time spent performing ‘near’ activities with these two approaches (range of mis-reporting: +3.13 hours (over-reported) to -5 hours (under-reported), Figure 4.4). These differences did not reach statistical significance, possibly due to the relatively small subject numbers (p=0.59). Myopes and non-myopes also appear to mis-report their daily time spent performing ‘near’ activities by a similar amount, as evident in Figure 4.4.

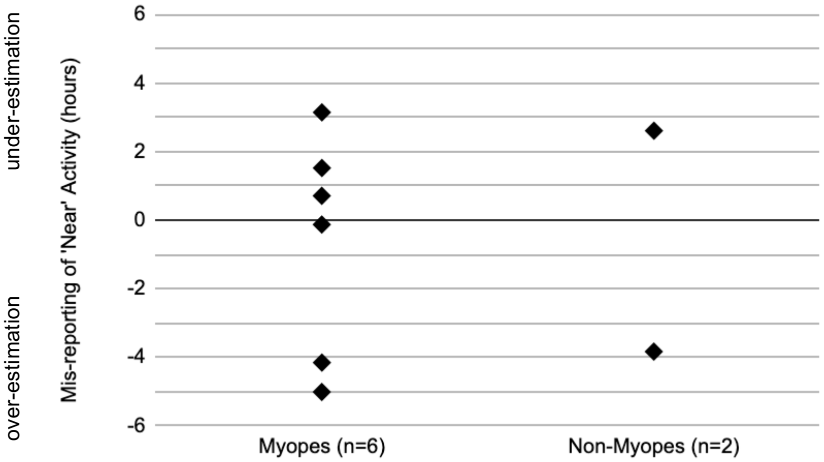

Figure 4.4: Subjective vs 'Objective' Reports of 'Near' Activity. A small sample of myopes (n=6) and non-myopes (n=2) both mis-reported their 'near' activity on subjective questionnaires, by a substantial amount.

During an AP, the amount of daily 'near' activity performed on average, as indicated by the daily Actiwatch inputs, was generally quite variable across participants (range: 4 to 14.7 hours, mean: 7.69 (2.22) hours). In terms of average daily hours of 'near' activity performed by myopes versus non-myopes, no significant difference was found (7.82 (2.31) and 7.49 (2.12) hours, respectively, p=0.64). There was also no relationship between average daily 'near' activity reported and SER or AL ($R^2 \leq 0.08$, Figure 4.5).

Median habitual WDs during sustained computer work were derived from photobooth recordings made during an AP for some participants. Here also, the data was generally quite variable (range: 15.99 to 65.28 cm, mean: 45.49cm), with some participants using their laptops at particularly close working distances and others a more intermediate working distance. However, individual participants, regardless of myopia status, showed minimal variation in their WD across the recording period (mean SD of WD: myopes, 4.42 cm; non-myopes, 4.76 cm). There was no significant difference in the median habitual WD between myopes and non-myopes (median WD: 46.43 and 43.97 cm, respectively, p=0.52). Moreover, there was no relationship between habitual "computer" WD and either SER or AL ($R^2<0.02$, Figure 4.5).

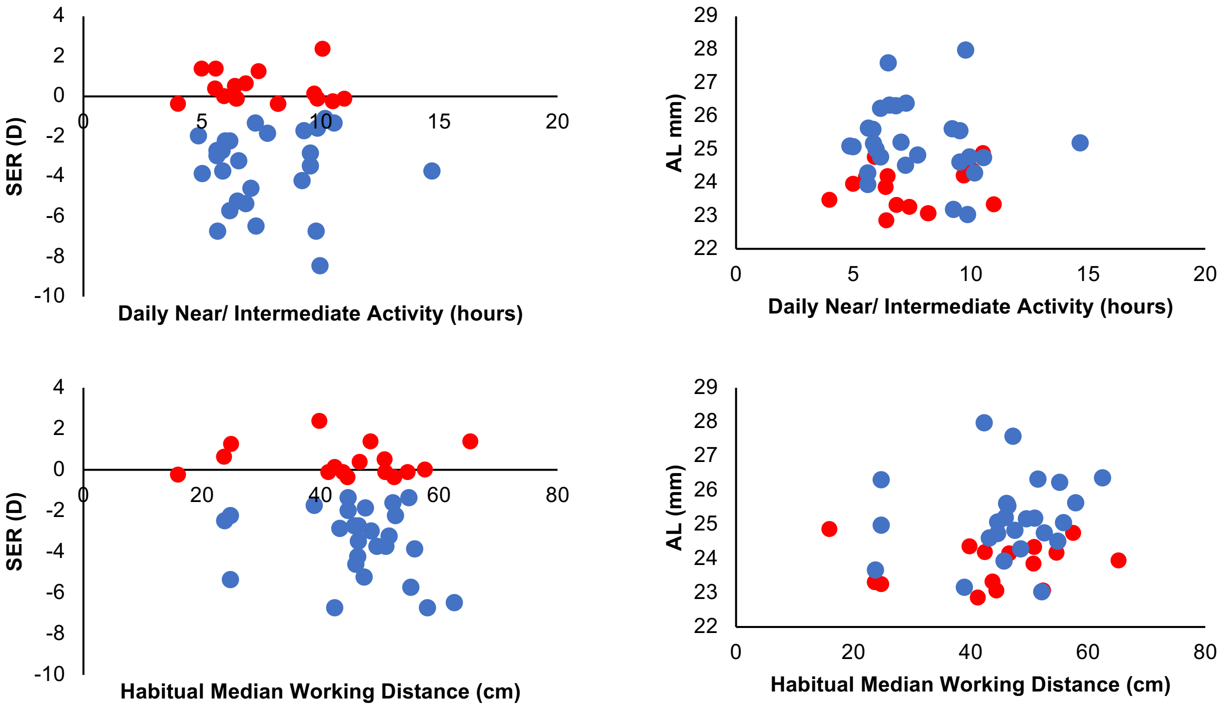

Figure 4.5: 'Near' Behavior in Myopes and Non-Myopes. The mean daily 'near' activity reported top panel) and habitual intermediate working distance (bottom panel) was similar in myopes (blue) and non-myopes (red) and had no significant correlation with SER (left panel) nor AL (right panel).

A comparison of the 'near' behavior during academic and non-academic periods in the subset of participants for which observations were made in both periods (n=14, Figure 4.6), revealed that participants performed significantly less 'near' activity during the NAP (by on average 1.5 hours, p=0.02). On average, non-myopes and, to a lesser extent, myopes tended to spend less time on 'near' activities during the NAP compared to AP (mean reduction: non-myopes, 2.09 (1.73) hours; myopes 1.27 (2.32) hours); however this difference was not statistically significant (p=0.49). Interestingly, all non-myopes reported less 'near' activity in the NAP (range: 0.27 to 3.93 hours less), while reports from myopes were more variable, with some reporting more near activities (by 0.27 to 2.50 hours) and others less (by 0.56 to 6.28 hours) during the NAP (Figure 4.6). However, when using computers, their habitual WD showed no significant difference in between the two periods (on average difference: -1.91 cm, p=0.52).

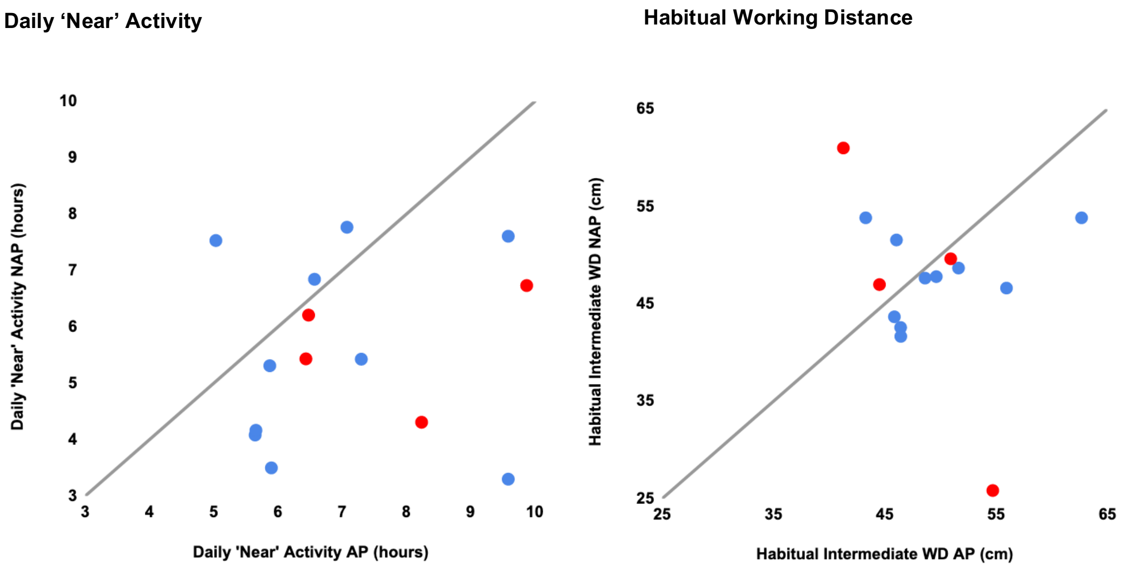

Figure 4.6: 'Near' Activity Changes with Academic Period. In participants with observations in both periods (n=14), an increase in the amount of daily 'near' activity was observed in the AP compared to the AP (by 1.5 hours, on average, p=0.02). There was no difference observed in the habitual intermediate working distance (WD) between the NAP and AP (mean difference: 1.91 cm, p=0.52).

Indoor Activity and Choroidal Thickness

Choroidal thickness (ChT) data were obtained for 46 of 49 participants during an AP. Data from the subfovea and 2250 μm nasal (N) and temporal (T) to the fovea are shown in Figure 4.7. With respect to indoor behavior metrics during the AP, there was no relationship between either indoor interval frequency or duration and ChT at any of the above locations (data not shown, all $R^2 \leq 0.10$). ChT also appeared unaffected by the amount of 'near' activity performed on a daily basis, as tracked via the Actiwatch, for both myopes and non-myopes (data not shown, all $R^2 \leq 0.10$).

With respect to indoor lighting characteristics, there was also no significant relationship between ChT and indoor lighting brightness in myopes (all $R^2 \leq 0.03$), but within non-myopes increasing indoor illuminance was associated with thicker choroids (R^2 range: 0.06 to 0.19, Figure 4.7) and approached statistical significance at the subfoveal location (p=0.07). Also in the non-myopes, increasing indoor R:B ratio was associated with thinner choroids (R^2 range: 0.05 to 0.19, Figure 4.7) and approached statistical significance at the N2250 location (p=0.08).

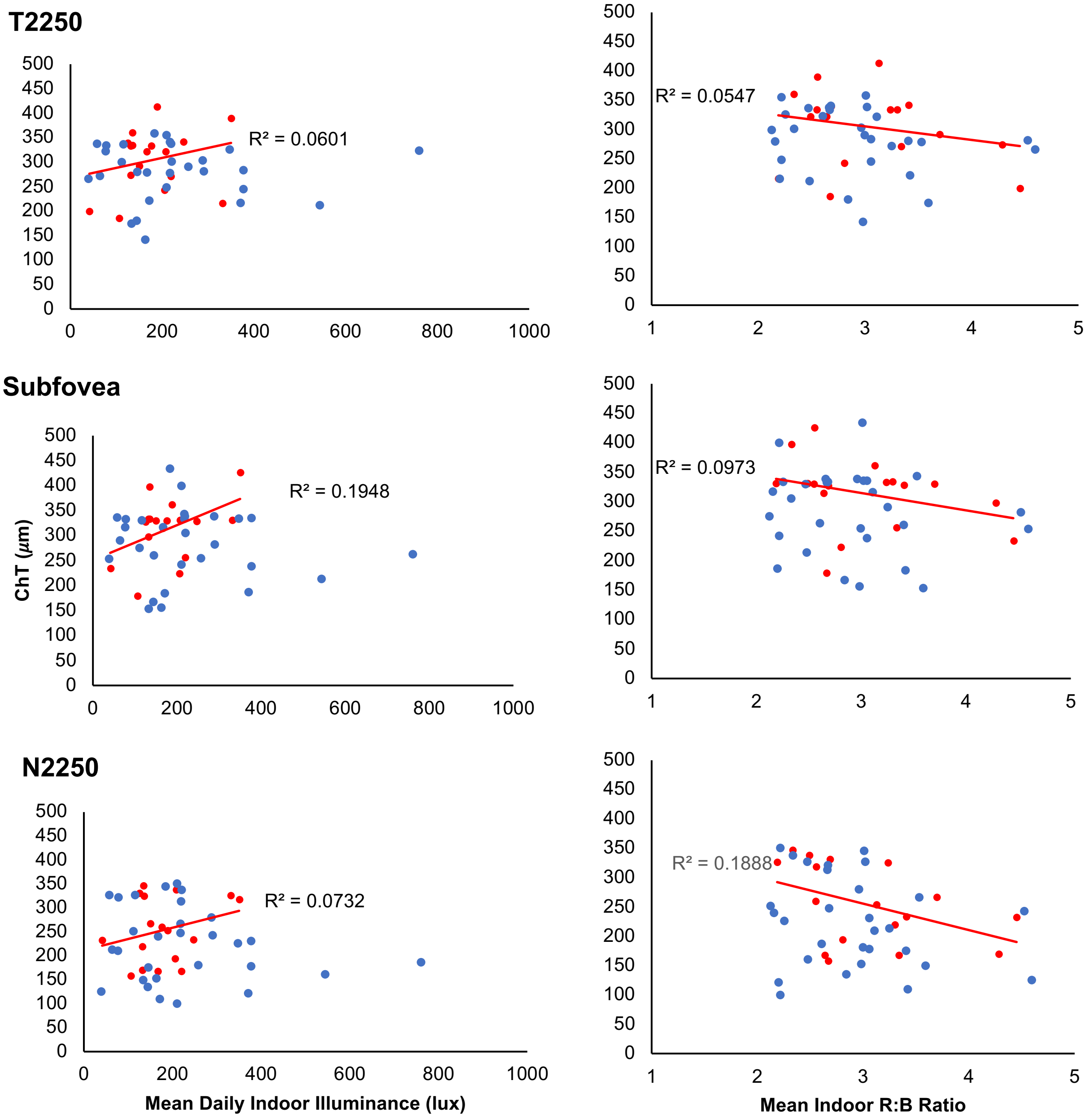

Figure 4.7: Indoor Lighting Characteristics and Choroidal Thickness. In general, mean indoor illuminance (left panel) was not related to ChT, except in non-myopes (red) where increasing illuminance was associated with thicker choroids, approaching statistical significance at the subfoveal location (p=0.07). Increasing indoor R:B ratio (right panel) was related to thinner ChT in non-myopes, and approached statistical significance at the N2250 location (p=0.08).

DISCUSSION

The study described here made use of an objective wearable technology (Actiwatch Spectrum Pro) and was part of a larger study to more comprehensively investigate the potential influences of outdoor and indoor behaviors on myopia presence and magnitude. Although two other groups have used this device in human myopia studies (Ostrin et al., 2018; Read et al., 2015), no attempts were made to characterize indoor behaviors. In fact, while much attention has been made to the possible protective role of outdoors against myopia development, no attention has been paid to quantifying indoor behaviors, including lighting characteristics, even though the proportion of time spent indoors far exceeds that spent outdoors.

The results presented here suggest that the dosing of indoor activity, in terms of mean daily indoor interval frequency and duration during an academic period, was not related to myopia presence, amount, or eye length. In addition, there was no difference in the dosing of indoor activity between academic and non-academic periods. However, the temporal dynamics of the indoor experience are only one part of the picture and may not be as important as the nature of the indoor environments experienced. To that end, we found that while the overall illuminance (brightness) of the indoor environment was not related to myopia presence or magnitude, it was linked to thicker choroids in non-myopes. In addition, warmer lighting (expressed as an increased R:B ratio) was associated with higher myopia and longer eyes within myopic participants, and to thinner choroids in non-myopic participants.

There are some important differences to consider in the indoor versus outdoor lighting characteristics experienced by our participant cohort. As discussed in the previous chapter outlining our results with respect to outdoor behaviors and myopia, bright light has been shown to thicken the choroid in both animals (Hung et al., 2018b; Lan et al., 2013) and humans, albeit to a lesser extent (Read et al., 2018). While no relationship between outdoor illuminance and choroidal thickness was found (Chapter 3), brighter indoor lighting was found to be associated with thicker choroids in non-myopic participants. Nonetheless, how this finding relates to previous animal work is not clear, as the ‘bright’ lighting used in such animal studies is generally well above that experienced indoors (e.g. 10,000 lux vs < 1000 lux). Indeed, in the current study, a cut-off illuminance of 1000 lux, was used to distinguish between outdoor and indoor activities. In addition, while the R:B ratio was, on average, greater when participants were outdoors, outdoor R:B ratio was not related to either myopia presence or magnitude, or to choroidal thickness, yet the opposite was true for indoor R:B ratio. These contrasting results for indoor and outdoor experiences highlight the importance of further study of indoor environments towards better understanding the risk factors for myopia development and/or progression.

The idea that proportionally longer wavelengths could stimulate eye growth due to the phenomenon of longitudinal chromatic aberration, whereby longer wavelengths come to focus beyond shorter wavelengths, has been investigated within animal myopia models. However, as discussed in the previous chapter, rearing animals in red monochromatic light appears to have differing, species-dependent effects on eye growth (Foulds et al., 2013; Gawne et al., 2018; Gawne et al., 2017a; Hung et al., 2018b; Liu et al., 2011; Qian et al., 2013; Rucker and Wallman, 2008; Smith et al., 2015). As part of such studies, the effect of the spectral composition of light on choroidal thickness has also been explored, but to a lesser extent. Interestingly, monochromatic red light has been shown to thicken the choroid in macaques (Hung et al., 2018b) and tree shrews (Gawne et al., 2017b), opposite to the predicted response based on chromatic aberration. However, it is important to note that such monochromatic conditions are not typical of the 'human' environmental experience. In the one study involving human subjects, brief morning exposure to blue-green light (500 nm) of illuminance 506 lux) using light therapy glasses has also been shown to thicken the choroid by a small amount (Read et al., 2018). Therefore, while results of this study as well as others, suggest that the choroid may be a biomarker of the eye's response to varying visual experiences, further work is required to understand the role of choroidal thickness modulation in eye growth.

The idea that near work could be a risk factor for myopia development is a longstanding one that has generated decades of mostly human research. Several aspects of near work have been investigated, including lags of accommodation, amount of near work, habitual working distance and gaze breaks, all of which are reviewed in detail in Chapter 1. Nonetheless, a recent meta-analysis found the amount of near work was not strongly related to myopia development in children (Huang et al., 2015). However, it should be noted that studies investigating the role of near work generally utilize subjective questionnaires, which are subject to recall and inherent bias. By utilizing the Actiwatch wearable technology, we were able to generate a more 'objective' measure of time spent in daily near/intermediate activities, by asking participants on a daily basis (1 hour before bedtime) to key in the hours of such activities performed that day. Based on this index of near/intermediate activity, no difference in the behavior of myopes and non-myopes during an academic period was found. Importantly, for the small cohort of participants who also reported their daily near/intermediate activity using a subjective questionnaire, there was substantial difference in the two measures of daily activities, on the order of hours, supporting the argument against the use of subjective questionnaire for quantifying behavior. Interestingly, participants who were observed in both academic and non-academic periods were generally found to undertake less near/intermediate work in the non-academic period. This finding offers a possible explanation for the observation in two different studies of slower myopia progression in the summer (non-academic period), although further investigation is required (Gwiazda et al., 2014; Tan et al., 2000).

Information about the working distances of participants used during computer-based tasks was obtained from videos recorded on the participants' computers. This approach served to ensure that the features of normal (habitual) behavior were captured, along with variability over time. In this sense, the approach is both novel and comprehensive in its approach to data collection. Surprisingly, regardless of myopia status, participants were found to maintain relatively stable working distances over sustained periods of computer work. However, habitual working distances were not related to either myopia presence or magnitude, or to choroidal thickness, although the inter-participant variability in working distances is large. None of these findings argue against the speculation from the study of Jewish scholars that close near works and/or rapid temporal variations in working distances might explain their increased risk of myopia (Zylbermann et al., 1993).

There are a number of strengths and limitations to consider in this study, many of which were summarized in the previous chapter in relation to the outdoor behavioral analyses. However, pertinent to the current indoor analyses, a significant strength is the fact that indoors was investigated at all. Given the substantial amount of time indoors compared to outdoors by all generations, including children, an objective characterization of the dynamics of indoor exposure, including relevant lighting characteristics, is important to our understanding of the human myopia condition. However, the significant limitation in our participant demographics, as previously discussed, make it challenging to generalize these results to an external population at risk for the development of myopia. Therefore, further work is warranted in a younger (pediatric) and more diverse population.

In conclusion, for the first time to our knowledge, indoor activity has been quantified in an objective and dynamic manner utilizing wearable technologies in a group of young adults. The variations in choroidal thickness, at least among non-myopes and in eye length, among myopes, that appeared linked to indoor lighting characteristics, including its spectral composition, warrants further investigation. That none of the indices of near work activity proved to be risk factors for myopia is perhaps not unexpected, given that participants were young adults. Further longitudinal studies in children are warranted to fully understand the possible role of indoor environments in modulating eye growth and myopia development and/or progression.

Conclusions and Future Work

Although genetics are known to play a role in myopia development, several potential environmental risk factors have been identified. Most notable are increased near work, in particular closer near working distances and reduced gaze breaks, as well as reduced outdoor activity. Novel, more objective methods of quantifying the dynamics of habitual indoor activity, including near work, and outdoor activity are on the horizon, as described within the research presented here. By comparing data collected with these methods to that collected using more traditional, subjective questionnaire methods we found that university students, even when sampled over a relatively short period of a week, significantly mis-report the time they spend outdoors, as well as in near activities. The further suggestion that mis-reporting biases may be differentially affected by myopia status raises concerns about the interpretation of previous studies describing differences between myopes and non-myopes in their subjective reports of habitual outdoor activity. In addition, we have utilized these objective methods to describe the dynamics of habitual outdoor and, for the first time, indoor activity in young university students. We found that young adult university students spend extraordinary amounts of time indoors compared to outdoors and that the dynamics of outdoor activity (frequency and duration of activity intervals) was very consistent across participants, particularly during an academic period, likely reflecting the prescribed behaviors of these students. While there appeared to be no relationship between the dosing of indoor and outdoor activity and the presence or magnitude of participant myopia, we did find that outdoor activity changes between academic and non-academic periods, such that individuals go outdoors more frequently and for longer periods in non-academic periods. This finding, although not related to participant myopia status, may be important to consider in future objective myopia studies investigating outdoor activity, such as planned in children.

Much attention has been paid to the possible role of bright light as a possible protective feature of outdoors, but we found no relationship between the illuminance of light experienced outdoors and myopia presence or magnitude. However, we did find that the spectral composition of lighting experienced both indoors and outdoors, expressed in terms of an R:B ratio, may be important to eye growth, such that exposure to proportionally longer wavelengths was related to greater myopia in myopic eyes and possibly thinner choroidal thickness in non-myopic eyes. A possible protective feature of outdoors not captured in the study described in this dissertation is the likely difference in the visual scene experienced indoors versus outdoors. This short-coming should be corrected through on-going work to develop light-weight, wearable head-mounted devices incorporating depth-finding cameras and wireless technologies, which should allow comprehensive characterization of the visual scenes in the habitual indoor and outdoor environments of individuals. Quantification of the nearness of objects to individuals and subsequent modeling of predicted retinal defocus patterns should thus be feasible. In addition, these wireless head-mounted technologies offer the possibility for the measurement of the lighting characteristics experienced at eye level rather than wrist level, a current limitation of the research presented within Chapters 3 and 4.

With respect to near work, we found that university students, on average and regardless of myopia status, perform about 1.5 hours more near/intermediate work a day during an academic period, compared to a non-academic period. During sustained computer tasks, their habitual working distance also did not vary with myopia status and remained quite stable across time. The recordings used for the latter analyses have the potential to also provide objective information about the dynamic gaze patterns of our participant cohort, with work towards developing a suitable automated image analysis program and further optimizing the methodology underway for use in future studies.

While the research presented here presents interesting new, and generally more objective data covering the behavior of university students than previously available, a major limitation is that the age of the study cohort, which was limited to young adults, carry a relative low risk of developing new myopia, if still emmetropic. Also myopia progression tends to be slower in this older age group compared to children. Along with the fact that our studies were cross-sectional in design, our findings were unlikely to provide new insights into the environmental risks factors important to the development and/or progression of myopia. That we uncovered few differences between our myopic and emmetropic cohorts is thus not surprising. However these studies provided the opportunity to develop and validate wearable technologies that are currently being optimized for pediatric use within a longitudinal study observing the natural indoor and outdoor behaviors of children prior to or just after their development of myopia. In addition, these planned pediatric longitudinal studies will incorporate more sophisticated statistical analysis methods, including multi-factorial modeling with consideration to multiple hypothesis testing, to better understand the causal links between behavior and myopia.

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