Lifestyle Factors in Myopia Development

CLAIR A. ENTHOVEN

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Lifestyle Factors in Myopia Development

Leefstijlfactoren bij myopie ontwikkeling

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Part I

Introduction and design

General introduction and aims of the thesis

GENERAL INTRODUCTION

Refractive errors

Refractive errors (myopia, hyperopia and astigmatism) are caused by a mismatch between the optical components of the eye. The most important components are the cornea, crystalline lens and axial length. In the optimal state, light rays are converged by the corneal curvature and crystalline lens and the focal plane falls exactly on the retina. This state is called emmetropia. In hyperopia, the focal plane falls behind the retina because the axial length is too short relative to the corneal curvature and lens power. In myopia, the focal plane falls in front of the retina because the axial length is too long (Figure 1).[1] Glasses or contacts with convex and concave lenses, respectively, are needed to correct hyperopia and myopia and achieve sharp vision.

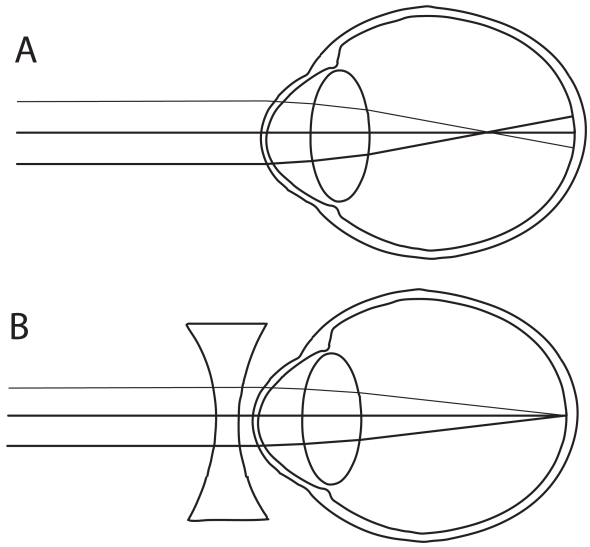

Figure 1. Refractive state of myopic eye (A), and corrected myopic refractive error (B).

Burden of disease

The prevalence of myopia (≤-0.5 diopter) in young adults has increased dramatically from 15% to 50% in Europe, and from 20% to 80% in East Asia in the last decades.[2, 3] An early age of onset in childhood will lead to higher degrees of myopia in adolescence and adulthood.[4, 5] High myopia (≤-6 diopter) in adulthood is in turn associated with a number of ocular complications such as myopic macular degeneration, retinal detachments, open angle glaucoma and cataract.[6] A third of the persons with high myopia will eventually develop bilateral visual impairment

or even blindness.[7] The apparent benign disorder therefore becomes a major public health problem. Whether low (≤-0.5 to -3 diopter) or moderate (≤-3 to -6 diopter) myopia also indicate an increased risk of complications is yet to be investigated.

Education and near work

In the beginning of the 19th century, it was noticed that myopia was more prevalent among those from higher classes of society.[8] The risk factors urbanization and education were observed a century later, and a link with near work was suggested.[9, 10] Only recently, evidence from Mendelian randomization studies advocated for a causal association between education and myopia.[11, 12] Level of education likely coincides with a cumulative amount of near work performed in childhood and adolescence, which is underscored by a strong association between reading distance in childhood and myopia progression.[13-16] The rapid rise of occupational computerization from the 80s onwards,[17] the more affordable personal computers in the 90s,[18] and the introduction of smartphones after 2000 suggested an increased risk of myopia due to screen time. However, the results from several studies on computer use and myopia so far were inconclusive.[19] The question whether smartphone use increases the risk of myopia needs more attention to slow down the growing eyes of the young generation.[20]

Outdoor exposure

In the beginning of the 21st century outdoor exposure was identified as a protective factor against myopia.[21, 22] Since then several randomized controlled trials have been performed to investigate a causal relationship between outdoor exposure and myopia. They all provided evidence that increased time spent outdoors reduces the risk of myopia incidence and progression in childhood.[23-25] Outdoor light intensity levels are much higher than indoor levels.[26] High light intensity increases dopamine secretion in the retina, which has been shown to reduce axial elongation in animal studies.[27] Current studies in children have only focused on school-based interventions to increase outdoor play. Whether non-school program interventions may be effective against myopia incidence is currently unknown.

Genetics

Genetic factors have long been known as contributor to myopia and refractive error development.[28, 29] Children with one or two myopic parents are more likely to become myopic than those with no myopic parents.[21, 30-32] Linkage studies identified a relatively low number (<50) of loci associated with (high) myopia from 1990 onwards.[33] After genome-wide association studies were introduced, the number of genetic variants associated with refractive error increased from only 1 associated locus in 2009 to 449 loci in 2020.[34, 35] All these genetic variants together explain 18.4% of the spherical equivalent phenotypic variance.[34] However, the fast increase in myopia prevalence can impossibly be due to genetic changes, influence of

environmental factors is more likely.[36] Gene-environment interactions have been identified with education in adult cohorts, but evidence for gene-environment interactions in children is scarce.[37-39]

Aims of this thesis

1. To determine the risk of pathologic consequences of low, moderate and high myopia (Chapter 2).
2. To explore the prevalence of spectacle wear, refractive errors and myopia from early childhood to adulthood (Chapter 3-5).
3. To investigate the association between screen time, outdoor exposure, and myopia (Chapter 6-8).
4. To examine the relation between genetic and environmental risk factors and myopia (Chapter 9-10).
5. To explain the social relevance of myopia for The Netherlands (Chapter 11-12).

Setting

The studies presented in this thesis were all embedded in observational population-based study cohorts.

The Generation R Study

The Generation R study is a prospective birth cohort study from fetal life until young adulthood in Rotterdam, The Netherlands.[40, 41] A total of 9778 mothers and their children were included between April 2002 and January 2006 during early pregnancy. Of the initial cohort, 6690 (68%), 5862 (60%) and 4929 (50%) children visited the research center at the age of 6, 9, and 13 years. At each visit, children underwent a detailed physical examination, and parents received questionnaires about the development and behavior of the children.

Preventive Child Healthcare Registry (PCHR)

The PCHR is a population screening as part of preventive child health care which was performed by Dutch public youth health organizations. These organizations cover a large area of the south of the Netherlands. The study population consisted of 99,660 children born between 2008 and 2015 who participated in vision screening around the age of 36, 45 and/or 60 months.

Rotterdam AMblyopia Screening Effectiveness Study (RAMSES)

RAMSES is a prospective population-based cohort study among children born between 1996 and 1997 in Rotterdam. Their vision was regularly measured as part of a Dutch screening program. Of the 4624 children at baseline, 2974 underwent a final eye examination at 7 years.[42]

Myopia App Study (MAS)

Teenagers aged 12 to 16 years old were recruited from six secondary schools in semi-urban areas in the Netherlands. Schools were asked to disseminate information on MAS among their pupils, and 300 teenagers from the first, second, and third grade consented to participate. App and ophthalmic measurements were performed between November 2018 until December 2019.

The Rotterdam Study

The Rotterdam Study is a prospective population-based cohort study of middle-aged and elderly subjects (45+ years of age) living in Ommoord, a suburb of Rotterdam, the Netherlands. The initial cohort started in 1989 and consisted of 7983 participants. The second cohort started in 2000 and consisted of 3011 new participants, and the third cohort started in 2006 and consisted of 3932 participants. Physical examinations were performed at 4-5 year intervals; lifestyle and behavioral factors were assessed by questionnaires.[43]

Avon Longitudinal Study of Parents and Children (ALSPAC)

ALSPAC is a prospective birth cohort study from fetal life until young adulthood from Avon, England. A total of 13,988 mother and their children were recruited between April 1991 and December 1992. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally and the total sample size increased to 14,901 children.[44, 45] The children visited the research center each year from the age of 7 onwards for a detailed physical examination, and their parents received questionnaires about the development and behavior of the children.

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Part II

Consequences of myopia

2

The complications of myopia: a review and meta-analysis

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ABSTRACT

Purpose: To determine the risk between degree of myopia and myopic macular degeneration (MMD), retinal detachment (RD), cataract, open angle glaucoma (OAG), and blindness.

Methods: A systematic review and meta-analyses of studies published before June 2019 on myopia complications. Odds ratios (OR) per complication and spherical equivalent degree (SER) (low myopia SER<-0.5 to >-3.00 D; moderate myopia SER ≤-3.00 to >-6.00D; high myopia SER ≤ -6.00D) were calculated using fixed and random effect models.

Results: Low, moderate, and high myopia were all associated with increased risks of MMD (OR=13.57, 95% CI=6.18-29.79; OR=72.74, 95% CI=33.18-159.48; OR=845.08, 95% CI=230.05-3104.34, respectively); RD (OR=3.15, 95% CI=1.92-5.17; OR=8.74, 95% CI=7.28-10.50; OR=12.62, 95% CI=6.65-23.94 respectively); posterior subcapsular cataract (OR=1.56, 95% CI=1.32-1.84; OR=2.55, 95% CI=1.98-3.28; OR=4.55, 95% CI=2.66-7.75 respectively), nuclear cataract (OR=1.79, 95% CI=1.08-2.97; OR=2.39, 95% CI=1.03-5.55; OR=2.87, 95% CI=1.43-5.73 respectively); and OAG (OR=1.59, 95% CI=1.33-1.91; OR=2.92, 95% CI=1.89-4.52 for low and moderate/high myopia respectively). The risk of visual impairment was strongly related to longer axial length, higher myopia degree and age over 60 years (OR=1.71. 95% CI=1.07-2.74; OR=5.54, 95% CI=3.12-9.85; and OR=87.63, 95% CI=34.50-222.58 for low, moderate, and high myopia in participants aged > 60 years, respectively).

Conclusions: Although high myopia carries the highest risk of complications and visual impairment, low and moderate myopia also have considerable risks. These estimates should alert policy makers and health care professionals to make myopia a priority for prevention and treatment.

INTRODUCTION

Myopia or nearsightedness is a refractive error caused by excessive axial elongation.[1, 2] Myopia can be corrected optically by glasses, contact lenses, or refractive surgery. Nevertheless, it has been associated with complications such as myopic macular degeneration (MMD), retinal detachment (RD), cataract, and open angle glaucoma (OAG).[3] These complications can lead to irreversible visual impairment later in life.[4]

The most important complication of myopia is MMD, which is a common cause of visual impairment particularly for high myopia.[5] Characteristics of MMD are lacquer cracks, Fuchs' spot, choroidal neovascularisation (CNV), or chorioretinal atrophy.[6] Posterior staphyloma is sometimes considered a specific type of MMD, while others consider it rather a risk factor for developing MMD.[6, 7] Common peripheral retinal lesions in high myopia patients are RD, pigmentary degeneration, lattice degeneration, and pavingstone degeneration, of which RD is the most sight-threatening.[5, 8] For cataract, the relationship with myopia is less evident. In particular nuclear cataract may result in a myopic shift, which hampers determination of the original refractive error.[9] Considering OAG, Perkins et al. already published in 1982 about a higher percentage of myopic patients in the OAG population.[10] A meta-analysis performed on 11 population-based studies also identified an increased risk of OAG for myopic persons.[11] Whether visual field progression in myopes is similar to other OAG patients is still unclear.

High myopia (spherical equivalent (SER) ≤-6D) is associated with reduced vision related quality of life and has significant socioeconomic impact.[12] The incidence of myopia and (high) myopia is rising globally and it is expected that the burden of its complications will lead to considerable visual morbidity in the near future.[13, 14] Myopia is already the most common cause of irreversible visual impairment in the working population. A recent study estimated 6 billion US dollars global productivity loss due to MMD, and this financial burden will undoubtedly become worse in the coming decades.[15, 16]

Although the association with myopic complications has been well established, precise risk estimates of MMD, RD, cataract, and OAG per degree of myopia are yet unknown.[17] In this review, we aim to provide a systematic review of the visual morbidity of myopia. First, we calculated the risk estimates of the most prevalent complications, i.e. MMD, RD, cataract, and OAG by performing meta-analyses on all existing data. Since data on other myopia related complications such as posterior staphyloma, retinoschisis and dome-shaped macula is limited, we did not include these in our review. Second, we explored the impact of these complications on best-corrected visual acuity (BCVA). Since cataract can be surgically treated, we also

investigated whether this procedure is safe and effective in myopic patients. The risk estimates derived from this study may create awareness among eye care providers for vision threatening complications associated with myopia, and help to inform myopic patients.

METHODS

We followed the guidelines of the PRISMA statement for the meta-analyses.[18] As published literature was used, ethical approval was not required.

Search methods

We conducted an extensive literature search in Pubmed on myopia and myopia related complications using the following MeSH terms: "Myopia", "Myopia, Degenerative", "Visual Acuity", "Retinal Degeneration", "Choroidal Neovascularization", "Retinal Detachment", "Cataract" and "Glaucoma". The complete PubMed search strategy is available in supplemental Table S1 and the PRISMA flow diagram is available in supplemental Figure S1. Titles and abstracts of articles, published before June 1st 2019, were independently reviewed for relevancy by two authors (AEGH and CAE) and included when the following criteria were met: (a) full text available, (b) written in English, (c) subject of article was myopia complications, visual consequences of myopia, epidemiology of myopia, or epidemiology of visual impairment. Any discrepancies between the two authors were solved by a thorough discussion with other experts until consensus was reached. A manual search was additionally performed by screening of the references of the included articles. All observational studies were considered for inclusion in the meta-analyses.

Data extraction and quality assessment

We obtained (i) geographic region of data collection, (ii) period of data collection, (iii) risk estimates of MMD, RD, cataract and OAG for myopia and different myopia categories, and (iv) visual acuity data of myopic patients with and without complications from each selected study. We assessed the quality of all studies using the criteria proposed by Sanderson et al. (2007).[19] The variables examined included the definitions of the exposures (any, low, moderate and high myopia), definitions of the outcome variables (MMD, RD, cataract and OAG), number of participants, age ranges, gender prevalence, study design and confounding factors used for adjustment. Crude odds ratios (ORs) were calculated for MMD when they were not reported in the studies, using the following formula:

$$OR = \frac{\text{myope with complication/myope without complication}}{\text{emmetrope with complication/emmetrope without complication}}$$

If the number of cases was zero, it was set to 1 for the OR calculation. Refractive error was categorized into five groups: no myopia (SER >-0.5D), any (SER ≤-0.5D), low (SER <-0.5 to >-3.00 D), moderate (SER ≤-3.00 to >-6.00D) and high (SER ≤ -6.00D), in line with the most recent classification system.[20]

Data synthesis

Meta-analyses were performed using a previously validated method in Microsoft Excel 2010; forest plots for all complications and myopia categories were constructed in GraphPad Prism 5.[21] A fixed or random effect model was used, depending on the number of included studies and the critical value of the calculated Q statistic on the χ^2 distribution. The Q statistic was calculated as the weighted sum of squared differences between individual study effects and the pooled effect across different studies. We calculated I^2 to investigate heterogeneity between studies, using the formula: ((Q-df)/Q)*100% (df represents degrees of freedom). We used a fixed effect model if heterogeneity was low, i.e. the calculated Q was lower than the critical value on a χ^2 distribution, and we used a random effect model otherwise.[21] Heterogeneity was considered as no, low, moderate or high for values of <25%, 25% to 50%, 50% to 75% and ≥75% respectively.[22]

RESULTS

Myopic macular degeneration

Prevalence of MMD

The prevalence of MMD in population-based studies varied from 0.2% in rural Central India, to 1.2% in Caucasian Australians and 4.0% in the Singapore Epidemiology of Eye Diseases (SEED) study (Table 1).[23-30] Definitions of MMD differed slightly among studies (Table S2). After stratification for myopia degree, the prevalence ranged from 13.3% to 65.4% in high myopes, 0.3% to 7.8% in moderate myopes and 0.1% to 7.0% in low myopes (Figure 1).[23-30] In six non-population-based studies focussing on high myopia patients only, MMD prevalence ranging from 8.3% to 64.0% was reported (Table S3).[31-36] A remarkably low MMD prevalence (<15%) among high myopia patients was reported in two studies.[33, 37] The first study was performed in a very young population, Singaporean men aged 19 to 25 years, and the second study was performed in asymptomatic Chinese patients aged 18 years and older, possibly explaining the low prevalence.[33, 37] The study of Zhao et al. (2018) included the most myopic and oldest participants of which 96.9% had at least a tessellated fundus and 54.5% also had diffuse, patchy or macular atrophy.[36]

Table 1. Characteristics of the studies investigating the relationship between myopia and myopic macular degeneration

Study	Authors	Country	Region	Data Collection Period	Total participants (n)	Study type	Age, years*	Male Gender (%)	Definition of Myopia (D)	Myopia (%)	High myopia (%)	Total MMD (%)	MMD definition (Table S2)
Blue Mountains Eye Study	Vongphanit et al. (2002)	Australia	Urban	1992-1993	3583	Prospective	67 (49-97)	43.5	Low: -1 to -3 Moderate: -3 to -5 High: ≤-5	16.8	2.7	1.2	a (excluding tessellation)
Beijing Eye Study	Liu et al. (2010)	China	53.9% urban, 46.1% rural	2001	4319	Prospective	57 (40-101)	45.8	Low: -0.5 to -2 Moderate: -2 to -6 High: ≤-6	23.3	2.4	3.1	a (excluding tessellation)
Handan Eye Study	Gao et al. (2011)	China	Rural	2006-2007	6603	Prospective	52 (>29)	46.4	Moderate: -0.5 to -5 High: ≤-5	26.6	2.1	0.9	a (excluding tessellation)
Shihpai Eye Study	Chen et al. (2012)	Taiwan	Urban	1999-2000	1058	Prospective	72 (65-91)	60.4	Any: ≤-0.5- High: ≤-6	30.8	4.2	3.0	b (≥M3; excluding tessellation)
Central India Eye and Medical Study	Jonas et al. (2017)	India	Rural	2006-2009	4561	Prospective	49 (30-100)	46.3	Any: ≤-1 High: ≤-8	16.6	0.5	0.02	c (excluding tessellation)
Hisayama Study	Asakuma et al. (2012)	Japan	Urban	2005	1892	Prospective	64 (>39)	41.0	Low: 0 to -2 Moderate: -2 to -6 High: ≤-6	49.0	3.7	1.7	d (excluding tessellation)
Chinese American Eye Study	Choudhury et al (2018)	United States	Urban	2010-2013	4582	Prospective	- (<49)	63	Low: -0.5 to -2 Moderate: -2 to -5 High: ≤-5	32.2	8.0	3.1	c (excluding tessellation)
Singapore Epidemiology of Eye Diseases (SEED) study	Wong et al (2018)	Singapore	Urban	2004-2011	8716	Prospective	57 (40-80)	49.6	Low: -0.5 to -3 Moderate: -3 to -5 High: ≤-5	35.7	6.0	4.0	c (excluding tessellation)

* *mean (range); D = diopter*

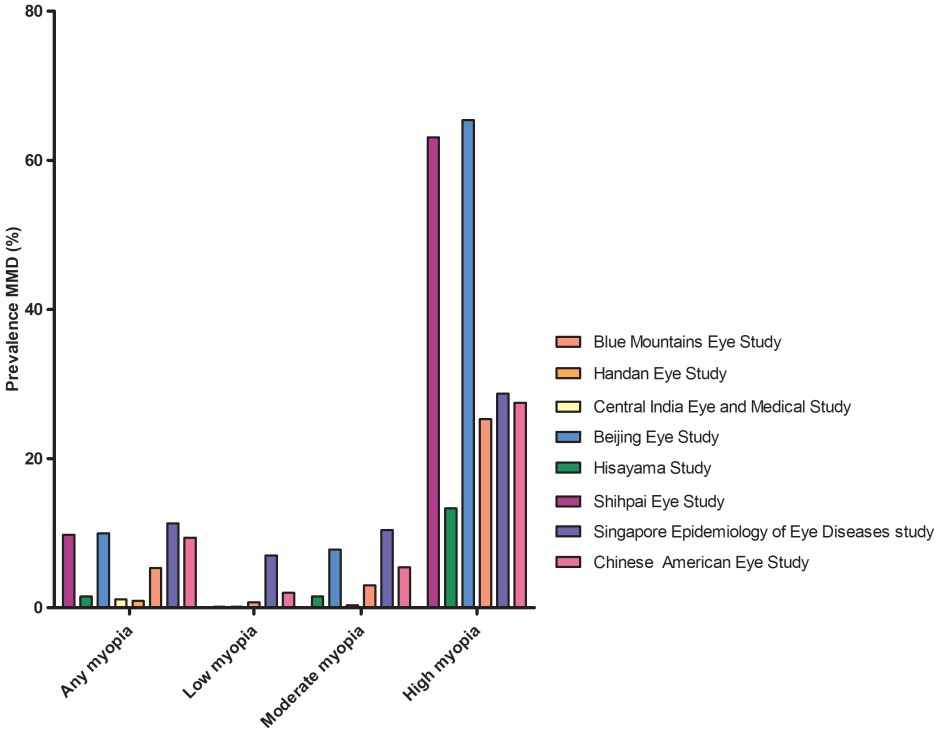

Figure 1. Prevalence of myopic macular degeneration among groups with any, low, moderate and high myopia derived from eight population based studies.

Our meta-analyses, including eight population-based studies, revealed an increased OR for any myopia (OR=102.11, 95% CI=52.60-198.22, moderate heterogeneity); low myopia (OR=13.57, 95% CI=6.18-29.79, high heterogeneity); moderate myopia (OR=72.74, 95% CI=33.18-159.48, moderate heterogeneity); and high myopia (OR=845.08, 95% CI=230.05-3104.34, no heterogeneity). (Figure 2).[23-30] The association between axial length and MMD was investigated in three studies. In a Russian population based study, patients with MMD had a 1.22 mm increased axial length compared to those without MMD.[38] In the Chinese American Eye Study, 80.4% of the participants in the fourth quartile of axial length (AL ≥25.60mm) had a particular lesion (MMD including tessellation, tilted disc and parapapillary atrophy), while in the third (AL 24.65-25.60 mm), second (AL 23.85-24.65 mm) and first quartile (AL <23.85mm) the percentage was 50.1%, 31.9% and 17.3% respectively.[30] In the Hisayama study, MMD (excluding tessellation, tilted disc and parapapillary atrophy) was only observed in eyes ≥23.0mm in men and ≥22.0mm in women, and the discriminating ability for the presence of MMD was highest at 25.9 mm in men and 25.3 mm in women.[39]

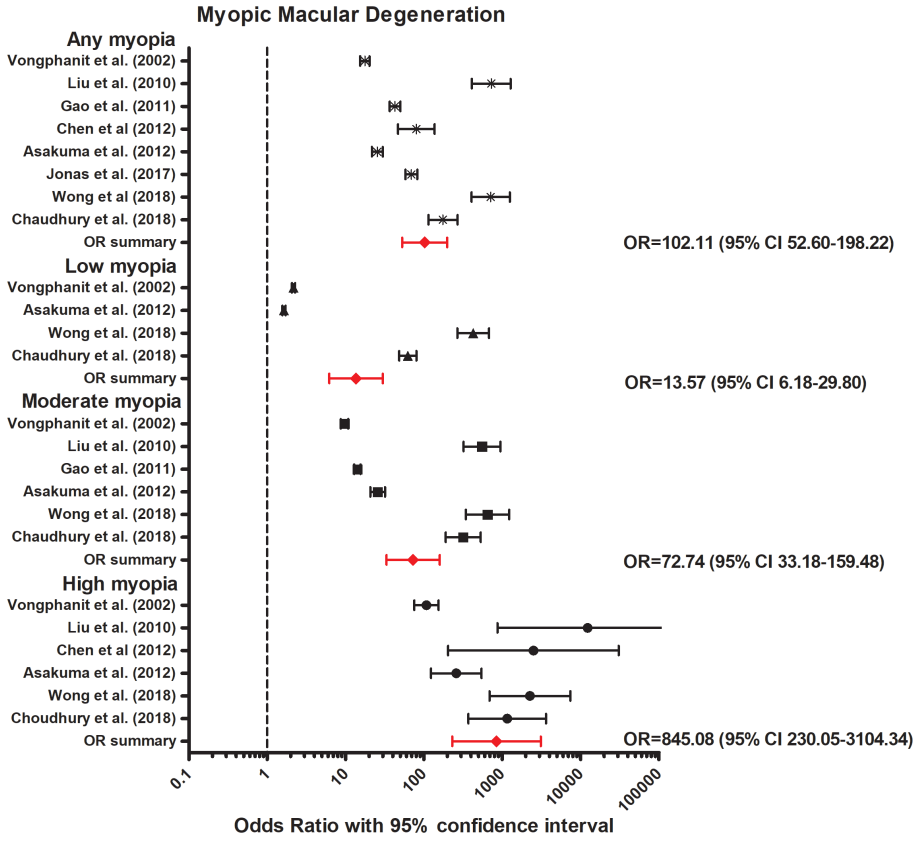

Figure 2. Forest plot of myopic macular degeneration in any myopia (Random Effect Model; Q=16.1; I^2=56.5); low myopia (Random Effect Model; Q=27.6; I^2=85.5); moderate myopia (Random Effect Model; Q=18.0; I^2=72.2) and high myopia (Random Effect Model; Q=5.2; I^2=4.3). Red lines with diamond represents the summary OR per myopia category. Summary OR for myopia categories are as follows: any myopia OR=102.11 (95% CI=52.60-198.22); low myopia OR=13.57 (95% CI=6.18-29.79); moderate myopia OR=72.74 (95% CI=33.18-159.48); and high myopia OR=845.08 (95% CI=230.05-3104.34).

Visual burden of MMD

BCVA was measured in eight studies; they all showed a worse BCVA in eyes with MMD compared to eyes without MMD (Table S4, Figure 3).[23-25, 27, 28, 36, 40, 41] Macular atrophy had the largest impact on BCVA, followed by CNV, patchy atrophy, diffuse atrophy or lacquer cracks according to a longitudinal study of MMD patients in Japan. Patients with only a tessellated fundus did not have a decreased BCVA.[42] Other studies also reported that patients with macular atrophy, CNV, or Fuchs spot had worse BCVA compared to those with patchy or diffuse atrophy, lacquer cracks or tessellated fundus (Figure 4).[23-25, 36, 41, 43] Progression of MMD to more severe stages was more frequent in older patients.[42]

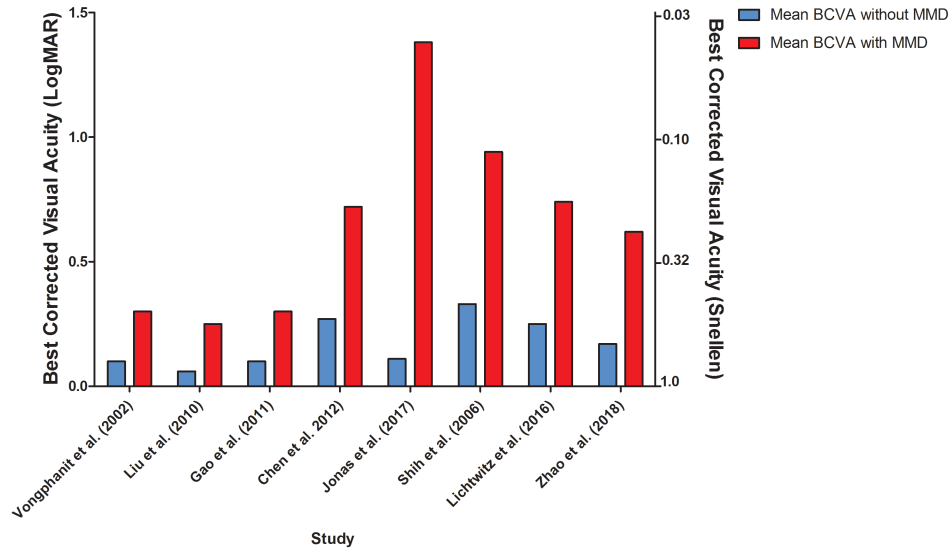

Figure 3. Best corrected visual acuity in eyes with and without myopic macular degeneration.

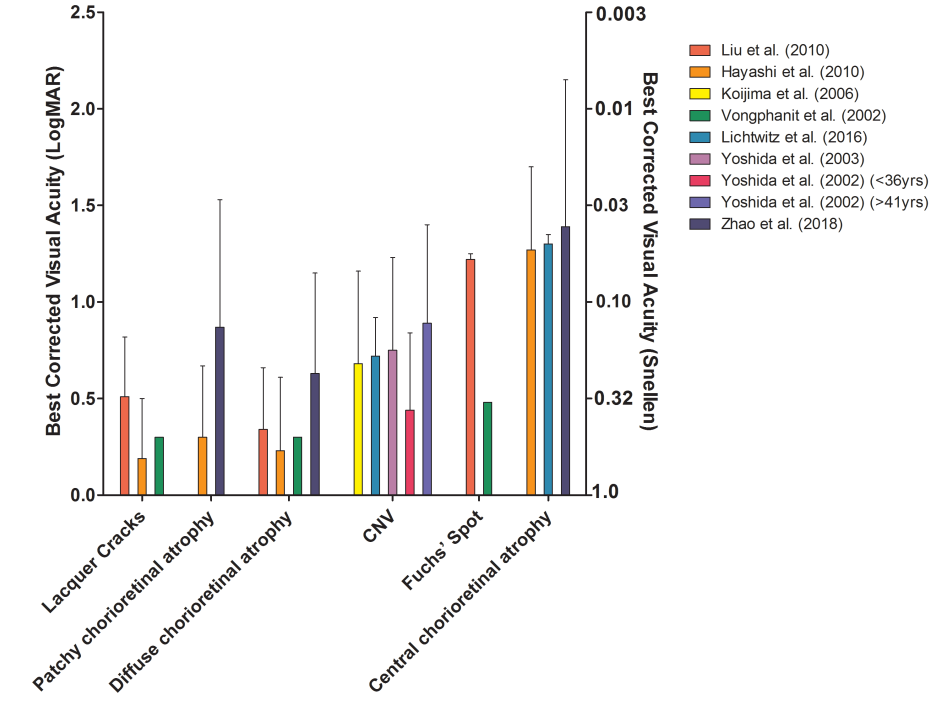

Figure 4. Best corrected visual acuity in eyes with different stages of myopic macular degeneration.

Retinal detachment

Incidence of RD

Annual incidence rates of RD ranged from 5.4 per 100,000 persons in Croatia (95% CI=4.1-6.4) to 16.5 per 100,000 persons in Japan (95% CI=15.0-18.1) (Table 2). Annual incidence of RD per degree of refractive error was only investigated by Burton et al (1989), reporting increased incidence rates of RD with decreasing SER from 3 in 100,000 persons with hyperopia (>0D) to 102 in 100,000 persons with high myopia (<-9D) (Table 2).[44] Five case-control studies were available for meta-analyses to determine the relationship between myopia and RD in various refractive error categories (Table 3).[45-49] All but one study showed a significant higher odds of RD for myopic persons (<0D) compared to non-myopic persons (Figure 5).[45-49] Pooled analyses revealed an increased OR for any myopia (OR=3.45, 95% CI=1.08-11.00, no heterogeneity); low myopia (OR=3.15, 95% CI=1.92-5.17, no heterogeneity); moderate myopia (OR=8.74, 95% CI=7.28-10.50, no heterogeneity); and high myopia (OR=12.62, 95% CI 6.65-23.94, no heterogeneity).

Visual burden of RD

Three studies reported BCVA after RD in myopic patients and they all concluded that visual prognosis was often worse in myopic RD compared to non-myopic RD.[46, 50, 51] The number of patients with post-operative BCVA of <20/200 was 34% in the high myopia group (SER <-6D) compared to 19% in those without high myopia.[50] Four studies reported on the association between myopia and reattachment of the macula after surgery. Two of these studies mentioned that reattachment of the macula after detachment was less successful in highly myopic patients, requiring more re-operations.[52-55]

Table 2. Annual incidence of retinal detachment

Authors	Country	Data Collection Period	Total RRD cases	Male Gender (%)	Age cases, years*	Annual incidence per 100,000
Laatikainen et al. (1985)	Finland	1978-1981	310	48.7	54.2±1.0 (5.7-83.0)	6.9 (5.5-8.7)
Törnquist et al. (1987)	Sweden	1971-1975 1976-1980	590	46.6	59.5 (-)	9.8 11.4
Li et al. (2003)	China	1999-2000	519	57	51 (median) (4-84)	8.0 (7.3-8.7)
Ivansevic et al. (1999)	Croatia	1988-1998	278	54.4	58.3±15.3 (7-89)	5.4 (4.1-6.4)
Haga et al. (2017)	Japan	2009-2011	897	62	54.4±15.5 (6-95)	16.5 (15.0-18.1)
Polkinghorne et al. (2004)	New Zealand	1997-1998	146	56.7	53.9±19.6 (5-96)	11.8 (9.8-13.7)
Mitry et al. (2010)	United Kingdom	2007-2009	1244	61.1	60-69 (median group)	12.1 (11.4-12.7)
Mitry et al (2011)	United Kindom	1987 1991 1996 2001 2006	-	-	-	10.1 (9.2-10.9) 11.0 (10.19-11.9) 12.5 (11.5-13.6) 12.2 (12.2-14.2) 15.28 (14.21-16.35)
Zou et al. (2002)	China	1996 1997 1998 1999	61	47.5	40-59 (median group)	11.3 14.1 14.1 17.9
Burton (1989)	United States	1976 1976 1976	172		55.9±17.9	3 (>0.00D) 15 (-0.10D to -6.00D) 102 (<-6.00D)
Chen et al. (2016)	Taiwan	2000-2012	2359	56.6	47.8 (47.1-48.4)	16.40 (15.34-17.46)

** mean±standard deviation (range); D = diopter*

Table 3. Characteristics of the studies investigating the relationship between myopia and retinal detachment

Authors	Country	Data Collection Period	Total participants (n)	Study type	Male Gender (%)	Age, years*	Definition of Myopia (D)	Adjusted covariates
Ogawa and Tanaka (1988)	Japan	1961-1985	12,837	Case-control	-	-	≤-0.75	Crude OR
Chen et al (2018)	China	2012	749	Case-control	100	21.2 (19-25)	≤-6.00	Crude OR
The Eye Disease Case-Control Study Group (1993)	United States	1986-1990	1,391	Case-control	47.4	- (21-80)	≤-1.00	Crude OR
Zou et al (2002)	China	1999	122	Case-control	-	-	<0.00	Crude OR
Chou et al (2007)	Taiwan	1995-2001	4569	Case-control	58.2	43±18.2	≤-1.00	Age and sex

** mean±standard deviation (range); D = diopter*

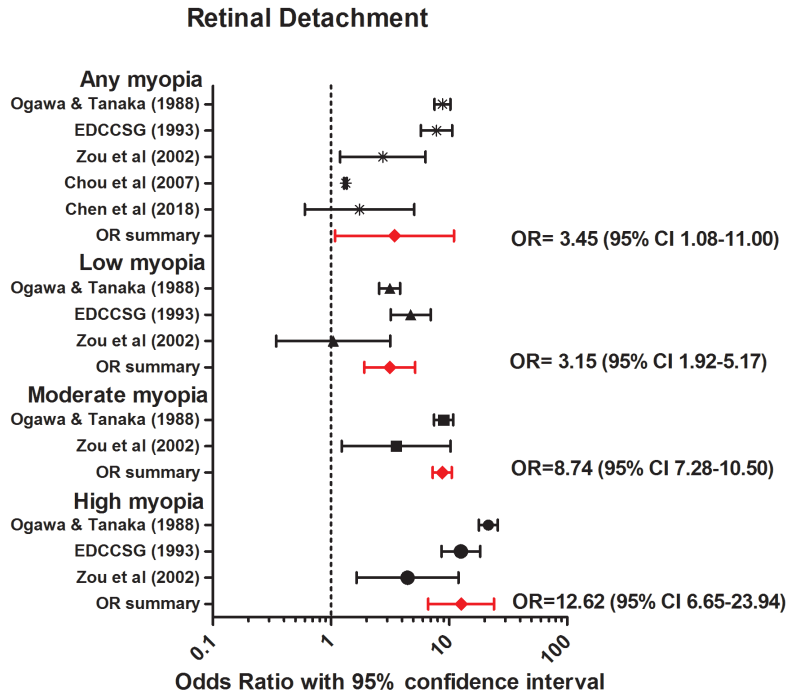

Figure 5. Forest plot of retinal detachment in any myopia (Random Effect Model; Q=1.7; I^2=0.0); low myopia (Random Effect Model; Q=3.7; I^2=0.5); moderate myopia (Fixed Effect Model; Q=2.8; I^2=0.6) and high myopia (Random Effect Model; Q=3.3; I^2=0.4). Red lines with diamond represents the summary OR per myopia category. Summary OR for myopia categories are as follows: any myopia OR=3.45 (95% CI=1.08-11.00); low myopia OR=3.15 (95% CI=1.92-5.17); moderate myopia OR=8.74 (95% CI=7.28-10.50); and high myopia OR=12.62 (95% CI=6.65-23.94).

Cataract

Myopia and development of various types of cataract

The association between myopia and incident or prevalent cataract was investigated in three prospective and eight cross-sectional studies (Table 4).[56-66] Nine out of eleven studies identified a strong association between myopia and posterior subcapsular cataract (PSC).[56-66] Our meta-analysis revealed a strong association for any myopia (OR=2.09, 95% CI=1.60-2.74, no heterogeneity), low myopia (OR=1.56, 95% CI=1.32-1.84, no heterogeneity), moderate myopia (OR=2.55, 95% CI=1.98-3.23, no heterogeneity), and high myopia (OR=4.55, 95% CI=2.67-7.75, no heterogeneity) (Figure 6). Seven out of the eleven studies reported an association between myopia and nuclear cataract; and our meta-analysis showed a significant association for any myopia (OR=2.51, 95% CI=1.53-4.13, no heterogeneity); low myopia (OR=1.79, 95% CI=1.08-2.97, no heterogeneity); moderate myopia (OR=2.39, 95% CI=1.03-5.55, no heterogeneity) and high myopia (OR=2.86, 95% CI=1.43-5.73, no heterogeneity). Regarding cortical cataract, neither prospective nor cross-sectional studies reported an association (Figure 7). Our meta-analysis showed a summary OR of 1.15 (95% CI=0.94-1.40, no heterogeneity) for any myopia, OR=0.99 (95% CI=0.85-1.15, no heterogeneity) for low myopia, OR=1.06 (95% CI=0.83-1.35, no heterogeneity) for moderate myopia and OR=1.07 (95% CI=0.81-1.40, low heterogeneity) for high myopia (Figure 8).

Table 4. Characteristics of the studies investigating the relationship between myopia and cataract

Study	Authors	Country	Data Collection Period	Total participants (n)	Study type	Ethnicity	Male Gender (%)	Age, years*	Definition of Myopia (D)	Adjusted covariates
Blue Mountains eye study (BMES)	Kanthan et al. 2014	Australia	1992-2004	2564	Prospective	-	43.3	66 (49-97)	Low -1 to ≥-3.5 Moderate -3.5 to ≥-6 High ≤-6	Age, sex
Salisbury Eye evaluation (SEE)	Chang et al. 2005	United States		2520	Cross-sectional	73.6% White 26.4% Black	42.1	73.0±5.1	Low: -0.5 to >-4 Moderate: -4 to >-6 High: ≤-6	Age, race, sex, tobacco use, education, and clustering between eyes
Beaver Dam Eye study (BDES)	Wong et al. 2001	United States	1988-1990	3053	Prospective	-	55.1	58.8±9.7	Low: -1 to -3 High ≤-3.25	Age, sex
Blue Mountains Eye Study (BMES)	Lim et al. 1999	Australia	1992- 1994	3654	Cross-sectional	-	43.3	66 (49-97)	Low: -1 to > -3.5 Moderate: -3.5 > -6 High:≤ -6	Age, sex
Singapore Malay Eye Study (SiMES)	Pan et al. 2013	Singapore,	2004	3280	Cross-sectional	Malay	-	- (40-80)	Low:-0.5 to ≥-2 Moderate: -2 to ≥-5 High: <-5.0	Age, sex, BMI, systolic blood pressure, HbA1c, smoking history, and education level
Singapore Indian Eye Study	Pan et al. 2013	Singapore	2007	3400	Cross-sectional	Indian	-	- (40- 84)	Any: ≤-0.5 Low: -0.5 to >-3 High: -3 to <-6	Age, gender, smoking, education, body mass index, hypertension, and total cholesterol level
The Casteldaccia Eye Study	Giuffrè et al. 2005	Italy	-	1068	Case-control	White	-	≥40	Any: >-1.5	None
The Barbados Eye Study	Wu et al.	Barbados	1997-2003	4036	Cross-sectional	Black	43	(40–84)	Any: <-0.5	Age, gender, SES, lens opacity
The Handan Eye Study	Duan et al.	China	2006-2007	6544	Cross-sectional	Chinese	46.3	52.0±11.8	Any: <-0.5	Not specified (age)
The Tanjong Pagar Survey	Wong et al.	Singapore	1997-1998	1029	Cross-sectional	Chinese	45.6	- (40-81)	Any: ≤-0.5 Low: -0.5 to >-3.00 Moderate: -3.0 to >-6 High: <-6	Age, gender, education, diabetes, and smoking status
The Visual Impairment Project	Mukesh et al.	Australia	1992-1999	2392	Prospective	Caucasian	45	62.5±10.9	Any: <-1.0	Age, sex, country of birth, occupation, smoking status, arthritis, diabetes mellitus, vitamin C supplements, calcium channel blockers.

** mean±standard deviation (range); D = diopter*

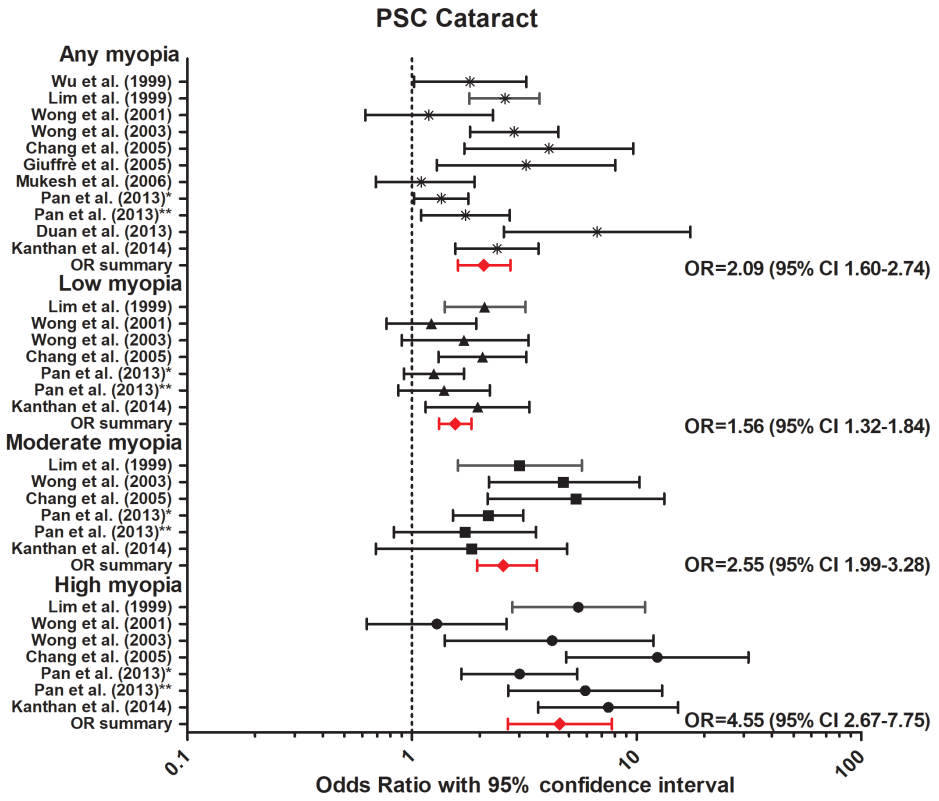

Figure 6. Forest plot of posterior subcapsular cataract (PSC) in any myopia (Random Effect Model; Q=11.6; I^2=13.8); low myopia (Fixed Effect Model; Q=7.5; I^2=19.7); moderate myopia (Fixed Effect Model; Q=7.5; I^2=19.2) and high myopia (Random Effect Model; Q=6.0; I^2=0.14). Red lines with diamond represents the summary OR per myopia category, which are as follows: any myopia OR=2.09 (95% CI=1.60-2.74); low OR=1.56 (95% CI=1.32-1.84); moderate OR=2.55 (95% CI=1.99-3.28); and high myopia OR=4.55 (95% CI=2.67-7.75). *represents Pan et al. 2013 Singapore Malay Eye Study. ** represents Pan et al. 2013 Singapore Indian Eye Study.

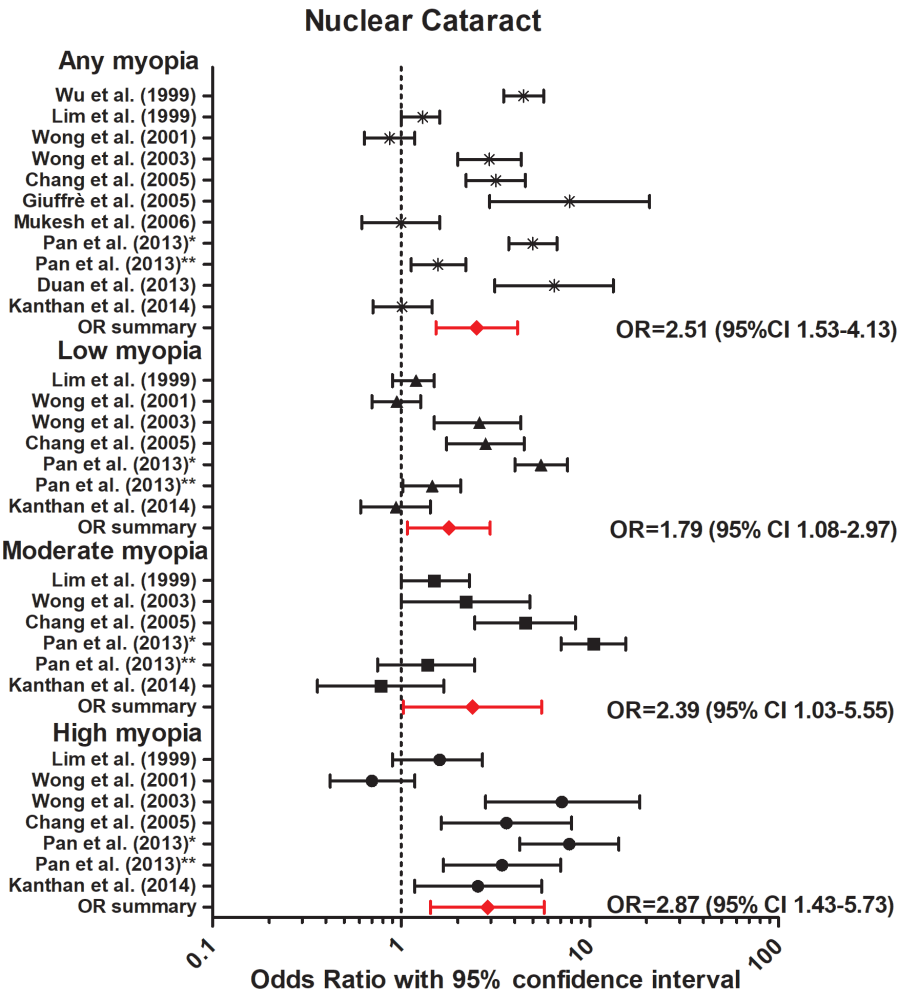

Figure 7. Forest plot of nuclear cataract in any myopia (Random Effect Model; Q=9.3; I^2=0; low myopia (Random Effect Model; Q=5.7; I^2=0); moderate myopia (Random Effect Model; Q=4.0; I^2=0.0) and high myopia (Random Effect Model; Q=5.0; I^2=0.0). Red lines with diamond represents the summary OR per myopia category, which are as follows: any myopia OR=2.51 (95% CI=1.53-4.13); low OR=1.79 (95% CI=1.08-2.97); moderate OR=2.39 (95% CI=1.03-5.55); and high OR=2.87 (95% CI=1.43-5.73). *represents Pan et al. 2013 Singapore Malay Eye Study. ** represents Pan et al. 2013 Singapore Indian Eye Study.

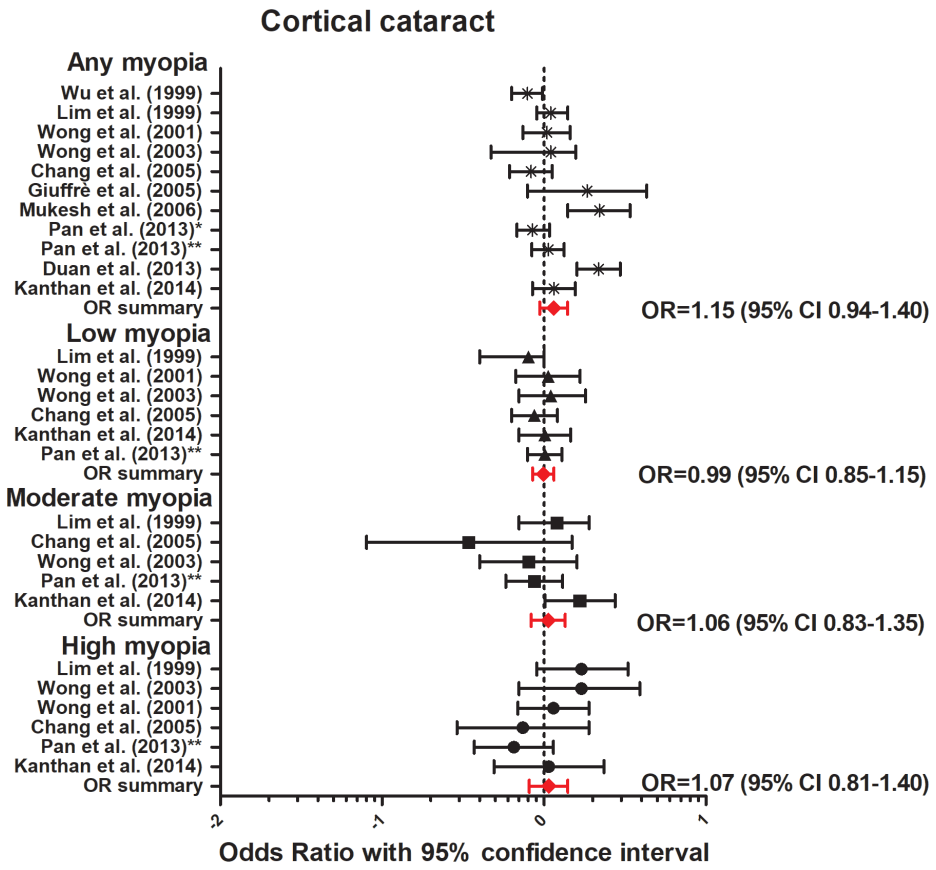

Figure 8. Forest plot of cortical cataract in any myopia (Random Effect Model; Q=11.5; I^2=12.8); low myopia (Fixed Effect Model; Q=0.9; I^2=0.0); moderate myopia (Fixed Effect Model; Q=7.15; I^2=30.1) and high myopia (Fixed Effect Model; Q=6.7; I^2=25.9). Red lines with diamond represents the summary OR per myopia category, which are as follows: any myopia OR=1.15 (95% CI=0.94-1.40); low OR=0.99 (95%CI=0.85-1.15); moderate OR=1.06 (95% CI=0.83-1.35); and high myopia OR=1.07 (95% CI=0.81-1.40). *represents Pan et al. 2013 Singapore Malay Eye Study. ** represents Pan et al. 2013 Singapore Indian Eye Study.

The risk of cataract extraction

To investigate whether cataract extraction (CE) is equally safe in myopic versus non-myopic patients, we included seven studies investigating the association between CE in myopic patients and development of RD after CE (Figure 9, Table S5). In five retrospective case series, prevalence of RD in myopic patients ranged from 0% to 3.84%.[67-71] Two case-control studies and one cohort study reported a significant risk of RD after CE in myopic patients (1.27% versus 0.28%, P<0.001; 8.0% versus 1.2% P<0.01 and HR=6.12; 95% CI 5.84-6.41), and the

association was stronger in patients undergoing CE aged below 55 years (HR=25.05, 95% CI=24.76-25.18).[72-74] The presence of posterior vitreous detachment prior to CE was not reported.[67-71, 73, 74]

OAG

The association between myopia and OAG

We performed a meta-analysis of 14 population based studies on the association between myopia and OAG (Table 5).[61, 66, 75-86] Diagnosis of OAG was based on visual field defects and optic disc aberrations in most studies. The overall OR was 1.95 (95% CI 1.74-2.19, no heterogeneity) for any myopia compared to emmetropia. The association became stronger with increasing myopia degree; the overall pooled OR was 1.59 (95% CI=1.33-1.91, no heterogeneity) for low myopia (>-3D) and OR=2.92 (95% CI=1.89-4.52, no heterogeneity) for moderate/high myopia (≤-3D) (Figure 10).

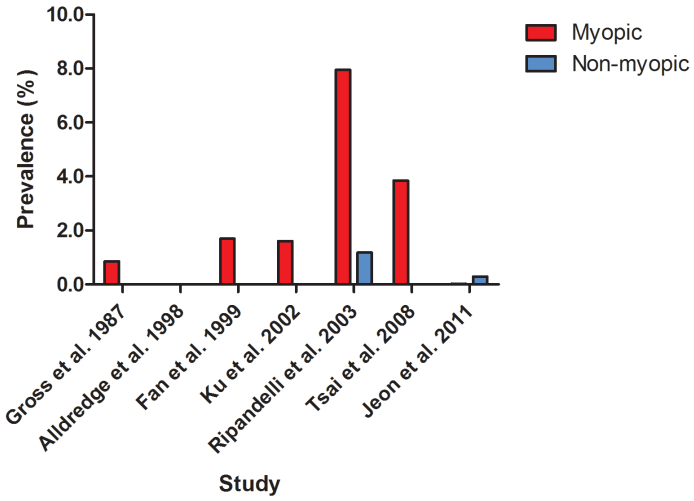

Figure 9. Prevalence of retinal detachment after cataract extraction in myopic patients. Horizontal axis represent different studies investigating retinal detachment rate. Two studies are case control studies (Ripandelli et al. 2013 and Jeon et al. 2011), the other five studies are retrospective case series. The vertical axis represent the prevalence of retinal detachment.

Table 5. Characteristics of the studies investigating the relationship between myopia and open angle glaucoma

Study	Authors	Data Collection Period	Total participants (n)	Study Type	Ethnicity	Age, years	Glaucoma definition	Definition of Myopia (D)	Adjusted covariates
The Barbados Eye Study	Wu et al.	1997-2003	4036	Cross-sectional	Black	40–84	GVFL, optic disc abnormalities	Any: <-0.5	Age, gender, SES, lens opacity
The Blue Mountains Eye Study	Mitchell et al.	1992-1994	3654	Cross-sectional	White	49–97	GVFL, CD-ratio ≥0.7 or asymmetry ≥0.3	Any: ≤-1.0 Low: ≤=1.0 to>-3.0 High ≤-3.0	Age, gender, family history, DM, steroid use, typical migraine history, hypertension, pseudoexfoliation
Visual Impairment Project	Weih et al.	1992-1996	4498	Cross-sectional	Diverse	≥40	IOP ≥22mmHg, GVFL, CD-ratio≥0.7 or asymmetry ≥0.3, family history of glaucoma	Any: ≤-0.5	Age, rural residence and family history
The Beaver Dam Eye Study	Wong et al.	1987-1988	4670	Cross-sectional	White	43–86	GVFL, IOP ≥22 mmHg, CD-ratio ≥0.8 or asymmetry ≥0.2, history of glaucoma treatment	Any: ≤-1.0 Low ≤=1.0 to>-3.0 High ≤-3.0	Age, gender
The Aravind Comprehensive Eye Survey	Ramakrishnan et al.	1995-1997	5150	Cross-sectional	Indian	≥40	GVFL, CD-ratio ≥0.9 or asymmetry ≥0.3, optic disc abnormalities, normal gonioscopy	Any: ≤-0.5 Low, moderate and high (no specific definition)	Age, gender, DM, hypertension, pseudoexfoliation
The Tajimi Study	Suzuki et al.	2000-2001	2874	Cross-sectional	Japanese	≥40	optic disc abnormalities, perimetric results, other ocular findings	Any: ≤-1.0 Low: ≤=1.0 to>-3.0 High ≤-3.0	Age, IOP
The Beijing Eye Study	Xu et al.	2001	4319	Cross-sectional	Chinese	≥40	Optic disc abnormalities, GVFL	Any: <-0.5 Low <0.5 to >-3 High (<-8)	Age, IOP
The Meiktila Eye Study	Casson et al.	2005	1997	Cross-sectional	Diverse	≥40	CD-ratio ≥0.7 or ≥0.6 with asymmetry ≥0.3, reduced NRRW, GVFL, >900 of TM visible	Any: <-0.5	Age, IOP, AL

Table 5. Continued

Study	Authors	Data Collection Period	Total participants (n)	Study Type	Ethnicity	Age, years	Glaucoma definition	Definition of Myopia (D)	Adjusted covariates
The Andhra Pradesh Eye Disease Study	Garudadri et al.	1996-2000	3724	Cross-sectional	Indian	≥40	Asymmetrical CD-ratio, NRRW reduced to 0.1, GVFL	Any: <-0.5	Age, DM, gender, IOP, hypertension
The Singapore Malay Eye Study	Perera et al.	2010-2013	3109	Cross-sectional	Malay	40-80	Optic disc abnormalities, GVFL	Any: ≤-1.0; Low ≤-1.0 to>-4.0 High ≤-4.0	Age, gender, IOP, education, height, CCT, hypertension, HbA1c
The Los Angeles Latino Eye Study	Kuzin et al.	2000-2003	5927	Cross-sectional	Latino	≥40	Optic disc abnormalities, GVFL	Any: ≤-1.0 Low ≤=1.0 to>-3.0 High ≤-3.0	Age, IOP, DM, gender, family history, NO, CP
National Health and Nutrition Examination Survey	Qiu et al.	2005-2008	5277	Cross-sectional	Diverse	≥40	GVFL	Any: ≤-1.0 Low: -1.00 to -2.99 High: ≤-3.0	Age, sex, ethnicity, income, and education.
Singapore Indian Eye Study	Pan et al.	2007	3400	Cross-sectional	Indian	40- 84	Optic disc abnormalities, GVFL	Any: ≤-0.5 Low: -0.5 to -2.99 High: ≤-3.0	Age, gender, education, hemoglobin A1c, total cholesterol level, intraocular pressure, and central corneal thickness in generalized estimating equation models
Korean National Health and Nutrition examination Survey	Chon et al.	2008-2011	13433	Cross-sectional	Korean	≥40	Optic disc abnormalities (CD-ratio ≥0.9), GVFL, or IOP>21 mmHG and VA <3/60	Any: ≤-1.0 Low: -1.0 to -2.99 High: ≤-3.0	Age, sex, income, and education.

D = diopter; GVFL = glaucomatous visual field loss; IOP = intra-ocular pressure; NRRW = neuro retinal rim width

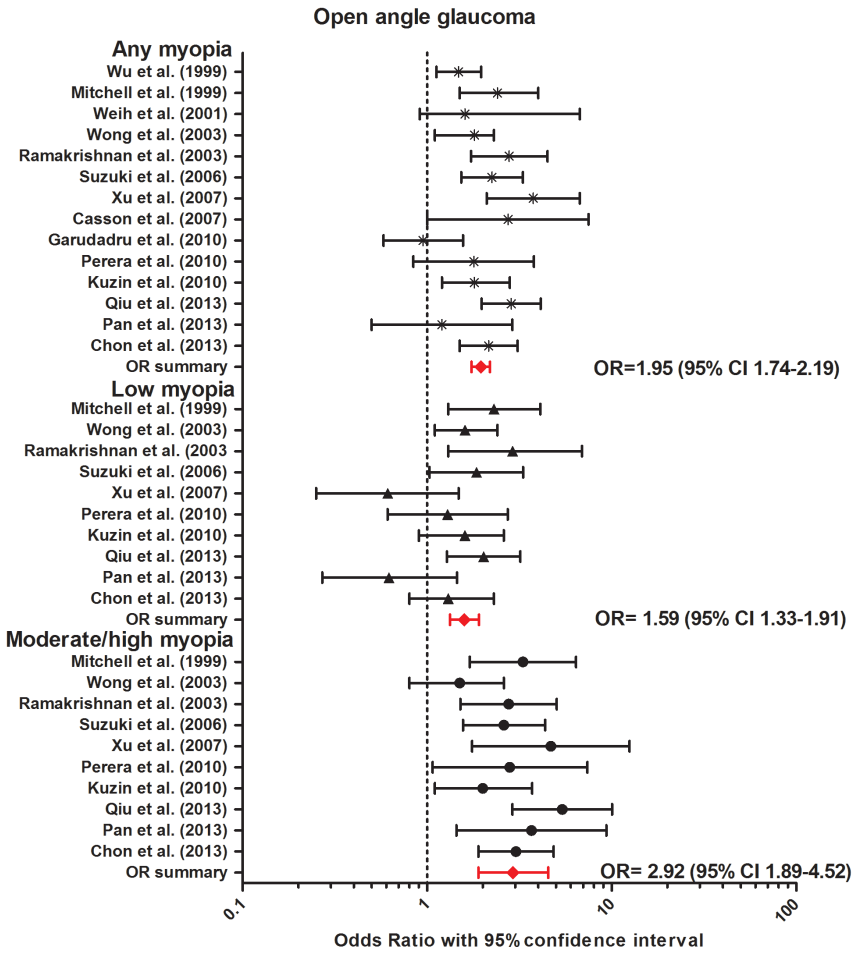

Figure 10. Forest plot of open angle glaucoma in any myopia (Fixed Effect Model; Q=8.3; I^2=0.0); low myopia (Fixed Effect Model; Q=0.3; I^2=0.0); and moderate/high myopia (Random Effect Model; Q=2.6; I^2=0.0). Red lines with diamond represents the summary OR per myopia category, which are as follows: any myopia OR=1.95 (95% CI=1.74-2.19); low OR=1.59 (95% CI=1.33-1.91); moderate/high OR=2.92 (95% CI=1.89-4.52).

Visual burden of OAG

Seven retrospective studies, five case only and two case-control studies, reported on the association between myopia and visual field loss progression (Figure 11 and Table S6). OAG patients with normotensive intra-ocular pressure under treatment were included in all studies and follow-up length ranged from 2 to 10 years. Myopia was identified as a risk factor for visual field progression in OAG in three studies.[87-89] However, the other four studies did not report an

association.[90-93] Whether progressive OAG is an important cause of myopic visual morbidity remains therefore questionable. Lack of data hampered investigation of the association between myopia and visual acuity in OAG patients.

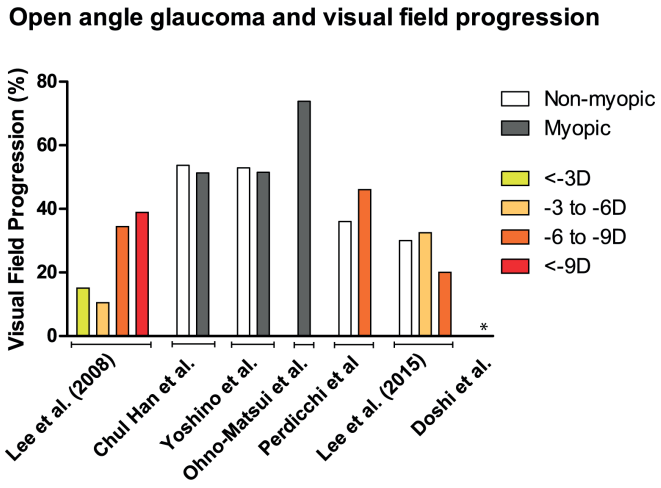

Figure 11. Overview of visual field progression (%) between non-myopic and myopic patients. Different refractive error categories were indicated by orange patterns. Patients were categorized as 'Myopic' if refractive error category was unavailable. Doshi et al. found 0% progression in the group SER ≤-6D.

Visual burden of myopia

Vision loss from any cause in myopia was investigated in only a few studies. A study using data from the Rotterdam Study, performed in the Netherlands, showed that 34.6% of the high myopes will eventually develop bilateral visual impairment (25.0%) or blindness (9.6%).[5] Visual impairment (VA <0.3 and VA ≥0.05) and blindness (VA<0.05) were defined according to the World Health Organization (WHO) criteria in this study.[5] The risk of visual impairment in high myopia started to increase already before the age of 60 years.[5] Another Dutch study, including population-based, family-based and case-control data, investigated the association between myopia, axial length and visual impairment. An overall risk of visual impairment was reported which increased myopia degree (OR=0.92, 95% CI=0.62-1.35 for SER -0.5 to >-3D; OR=1.71, 95% CI=1.07-2.74 for SER -3 to >-6D; OR=5.54, 95% CI=3.12-9.85 for SER -6 to >-10D; OR=7.77, 95% CI=3.36-17.99 for SER -10 to >-15D; OR=87.63, 95% CI=34.50-222.58 for SER <-15D in participants aged >60 years).[4] Axial length was a stronger predictor for visual impairment or blindness than refractive error. The cumulative risk of visual impairment or blindness increased from 6.9% in eyes less than 24 mm, up to 90.6% in eyes of 30 mm or greater in participants aged 75 years or older.[4] For those with axial length ≥26 mm, one in three

was at risk of developing bilateral low vision with increasing age. The rise in cumulative risk started at 55 years for participants with SER ≤-10D, and at 65 years for participants with SER -6D to -10D, and showed an almost exponential increase for SER ≤-10D thereafter (Figure 12).[4] Considering visual function, ten studies reported on ERG responses (multifocal and full field ERG) in mostly healthy adults with different axial lengths and identified decreased amplitudes of both a- and b-wave responses, correlating negatively with axial length.[94-103] Contrast sensitivity was only investigated in healthy myopic participants and multiple studies reported a decreased contrast sensitivity in myopic compared to emmetropic participants.[104-106]

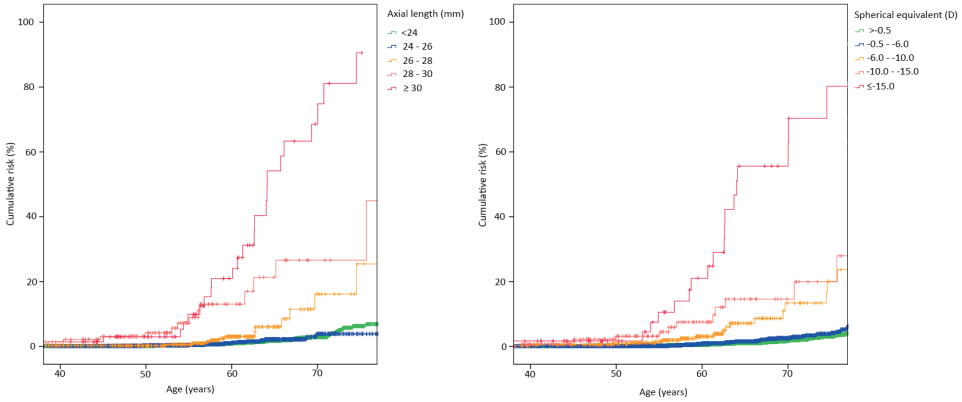

Figure 12. Kaplan-Meier curve of the cumulative risk of visual impairment with increasing age per category of axial length (left) and spherical equivalent (right) (from Tideman et. al, 2016).
JAMA Ophthalmol. 2016;134:1355–1363. © 2016 American Medical Association.

DISCUSSION

Our study showed that myopia is associated with MMD, RD, PSC, and OAG. The risk of these complications was not only increased for high myopia, but also for low or moderate myopia. Overall, myopic patients had a hundred-fold higher risk of MMD, three-fold higher risk of RD, three-fold higher risk of PSC and an almost doubled risk of OAG.

MMD was by far the most hazardous complication. Emmetropic eyes, which served as the reference, did not develop MMD, which hampered interpretation of the high risk estimates for myopes. Frequency data on MMD could be more informative, but non-uniform definitions, highly variable age distributions of study participants, and the potential selection bias due to hospital recruitment caused large heterogeneity in prevalence estimates. MMD prevalence ranged from 0.1% to 7% in low myopia, 0.3% to 10% in moderate myopia and 13% to 65% in

high myopia.[24-26, 29] BCVA was generally worse in patients with macular atrophy, CNV or Fuchs spot.[23-25, 36, 41, 43] Tessellation of the fundus did not influence visual acuity, but may increase the risk of more severe MMD with age.[42]

Our meta-analysis revealed an increased risk for RD in all myopia groups with higher risk for those with more severe myopia. The OR for moderate myopia was already 8.7, and given the relatively high frequency of myopes in this category, the RD prevalence is expected to rise dramatically. Frequency data of RD per degree of myopia were limited in literature, but Japan and Taiwan reported remarkably higher incidence rates of RD than other countries with a lower myopia prevalence.[14] This confirms the notion that RD rates will increase when myopia becomes more prevalent.[107] The visual prognosis of myopic RD appeared to be worse than non-myopic RD in some studies, but this needs more comprehensive research.[52-55]

Our meta-analysis identified a strong association between myopia, PSC and nuclear cataract, but not between myopia and cortical cataract. Three mechanisms have been proposed to explain the relationship between myopia and cataract. First, myopic eyes may be exposed to a higher level of oxidative stress caused by faster vitreous liquefaction, or by a decreased level of glutathione, an anti-oxidative agent in the lens of myopic eyes leading to cataract formation.[56, 108, 109] Second, the higher level of by-products of lipid peroxidation in myopia may increase cataract formation.[56, 110-112] Third, longer axial length may lead to diminished diffusion of nutrients from the posterior chamber to the lens causing cataract. This mechanism seems less plausible, because the aqueous humor also provides nutrients to the lens.[58] It should be noted that the association between myopia and nuclear cataract may be influenced by the myopic shift occurring with this type of cataract.[9] Cataract is a disorder which can be resolved rather easily by performing CE. In myopic patients, however, reports suggest an increased risk of post-surgery RD, as CE causes a disruption of the capsular-zonular diaphragm and vitreous traction of a thin peripheral retina may then predispose to RD in myopes.[69, 70, 113] However, the long interval between CE and RD in some studies makes a direct causal relationship unlikely.[72-74] The procedure itself may be more difficult. After vitreous removal in high myopes zonular weakness may occur, leading to potential zonular instability. In addition, sculpting maneuvers may be more difficult due to a deeper anterior chamber.[114] Given all considerations, when posterior vitreous detachment has taken place and substantial vision loss due to lens opacities is present, the visual benefits outweigh the risks and CE is recommended.[74] Nevertheless, careful pre-operative inspection for retinal tears and prophylactic treatment with laser is warranted.[67, 68, 73]

The positive association between myopia and OAG is in line with previous reports.[11] Distinguishing myopic optic neuropathy from OAG remains a challenge and may have led to misclassification and invalid estimations of the calculated OR.[115] Since myopic eyes have larger

optic disc sizes and therefore larger excavations, OAG is prone to misdiagnosis. The underlying mechanism for a predisposition to OAG is still unclear. Doshi et al. (2007) mentioned that longer axial length lead to tilting of the optic disc, and may possibly cause damage to the axons in the lamina cribrosa.[90] Taking into consideration the differences in study design and definitions myopic OAG may unlikely progress to central visual field defects.

To our knowledge, this is the first systematic review and meta-analysis about complications associated with myopia. One of the strengths is the completeness of our literature search. We believe that we included all observational studies performed from 1988 to 2019 in the meta-analyses. Another asset is the estimations of risk per refractive error category, which elucidated the profound risk increase for the higher degrees of myopia, but also revealed substantial risks for the much more common low and moderate myopia. Limitations of our study include the different definitions used for myopic complications, in particular for MMD and OAG. We strived to use the recently defined guidelines by the International Myopia Institute to optimize uniformity between studies, but sometimes had to apply best clinical judgement if this was not possible.[20] Our decisions may have affected the results. Another limitation was the lack of multimodal imaging to detect all retinal complications; most studies only used color fundus photographs. In particular retinoschisis, macular hole, different types of staphylomas, and peripheral lesions are better visualized with other imaging techniques such as OCT and wide-field imaging. We therefore chose to focus only on MMD, RD, cataract and OAG. We expect that future studies will provide more results using newer and multimodal imaging techniques. Lastly, although axial length is more closely related to myopic complications than refractive error, we could not study this for most complications as data on eye biometry were missing.

Regarding clinical management, the results from our meta-analyses suggest that vision threatening complications can appear from moderate myopia onwards. There is a strong relationship between myopia degree, age of the participant and visual impairment; more severe myopia results in an earlier onset of visual threatening complications.[4, 5] Therefore, both factors should be taken into account regarding screening programs and clinical guidelines. A period of 20 years between diagnosis and perimetric blindness was estimated for OAG patients with average visual field loss progression.[116, 117] A significant visual loss over a follow up period of 10 years was determined for the natural course of MMD.[40, 42] Considering the asymptomatic period and window of possible action before the onset of complications we advise an ophthalmological screen at the age of thirty in myopic patients with SER≤-10D and at the age of fifty in patients with SER -6D to -10D.

In conclusion, this literature review and meta-analyses provide detailed risk estimates of myopic complications. One in three high myopes is at risk of bilateral low vision with age. Low and moderate myopes are less likely to develop such a severe visual outcome; nevertheless,

they are at significant risk to develop MMD, RD, cataract, and OAG. This not only affects the individual patient, it has a major impact on health care and society, in particular since future generations may become even more myopic. Awareness of the complications of myopia among patients, physicians, and policy makers is crucial, and a global strategy for prevention and treatment of myopia progression should become a priority.

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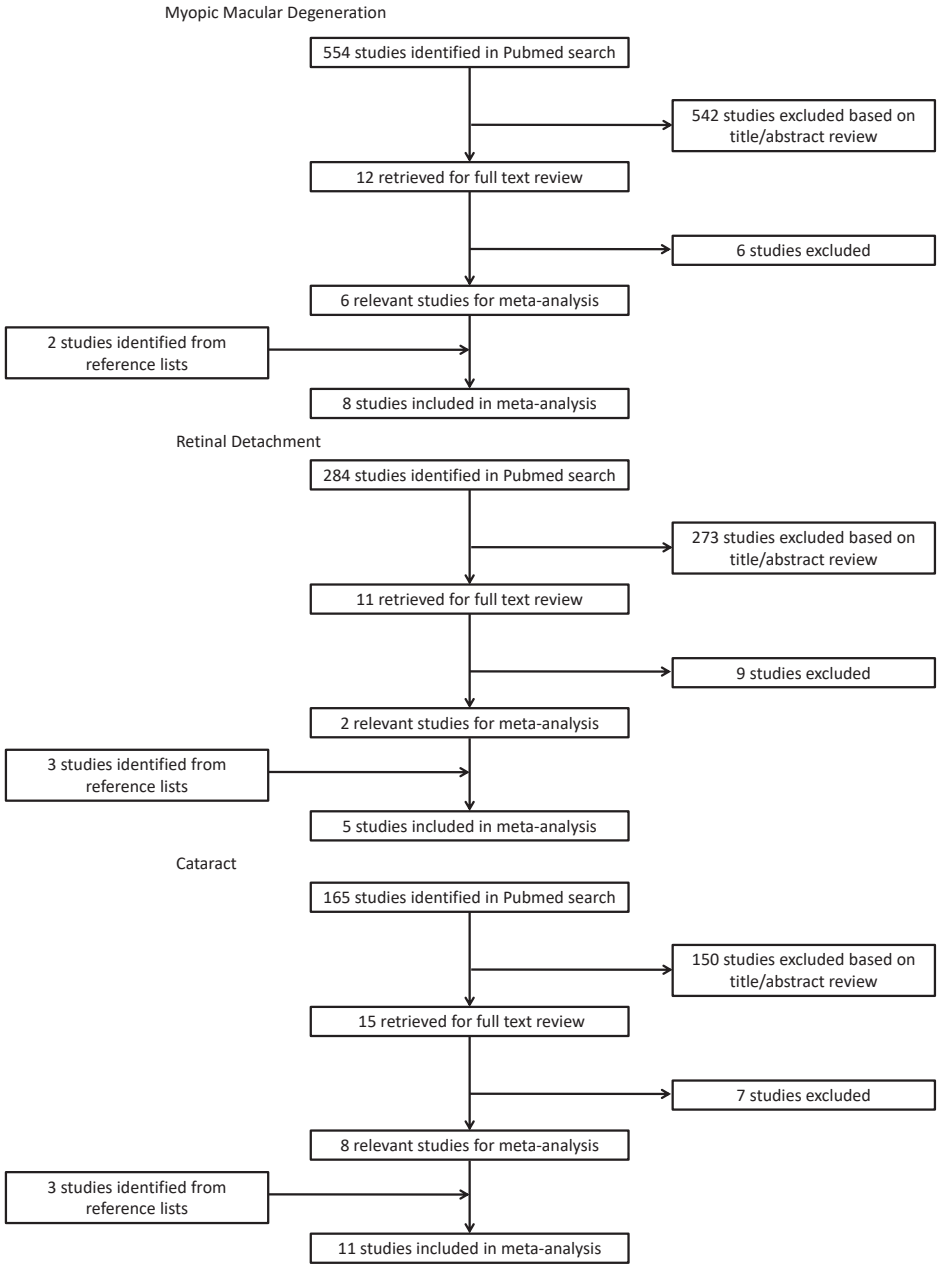
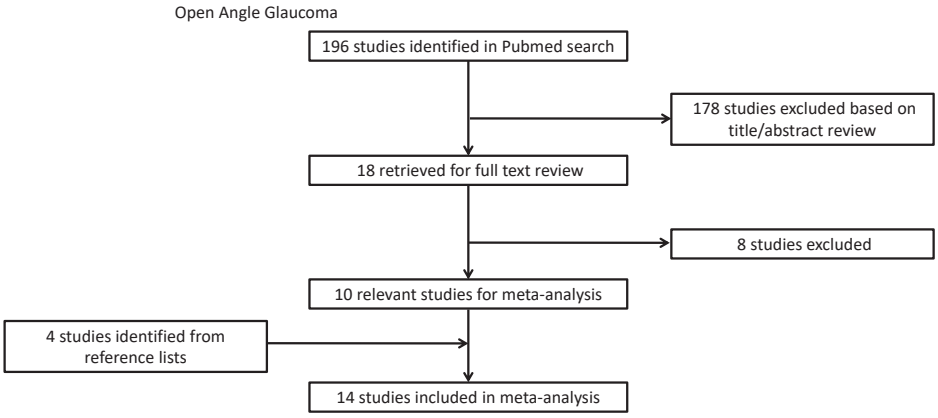
SUPPLEMENTS





Supplemental Figure 1. Flow diagram of literature search and selection process of articles for meta-analyses of the association between myopia and myopic macular degeneration, retinal detachment, cataract and open angle glaucoma.

Table S1. Search terms used in PubMed

Complication	Search terms PubMed (from 1900-01-01 to 2019-06-01; species: humans; language: English)
Myopic Macular Degeneration	("Myopia"[Mesh] OR "Myopia, Degenerative"[Mesh]) AND ("Cohort Studies"[Mesh] OR "Prevalence"[Mesh] OR "Incidence"[Mesh] OR "Case-Control Studies"[Mesh] OR "Cross-Sectional Studies"[Mesh]) AND ("Aged"[Mesh] OR "Middle Aged"[Mesh] OR "Adult"[Mesh]) AND ("Retinal Diseases"[Mesh])
Retinal Detachment	("Myopia"[Mesh] OR "Myopia, Degenerative"[Mesh]) AND ("Cohort Studies"[Mesh] OR "Prevalence"[Mesh] OR "Incidence"[Mesh] OR "Case-Control Studies"[Mesh] OR "Cross-Sectional Studies"[Mesh]) AND ("Aged"[Mesh] OR "Middle Aged"[Mesh] OR "Adult"[Mesh]) AND ("Retinal Detachment"[Mesh])
Cataract	("Myopia"[Mesh] OR "Myopia, Degenerative"[Mesh]) AND ("Cohort Studies"[Mesh] OR "Prevalence"[Mesh] OR "Incidence"[Mesh] OR "Case-Control Studies"[Mesh] OR "Cross-Sectional Studies"[Mesh]) AND ("Aged"[Mesh] OR "Middle Aged"[Mesh] OR "Adult"[Mesh]) AND ("Cataract"[Mesh])
Open Angle Glaucoma	("Myopia"[Mesh] OR "Myopia, Degenerative"[Mesh]) AND ("Cohort Studies"[Mesh] OR "Prevalence"[Mesh] OR "Incidence"[Mesh] OR "Case-Control Studies"[Mesh] OR "Cross-Sectional Studies"[Mesh]) AND ("Aged"[Mesh] OR "Middle Aged"[Mesh] OR "Adult"[Mesh]) AND "Glaucoma"[Mesh]

Table S2. Myopic Macular Degeneration classifications and definitions

Classification	Definition	Author (year)	Imaging
a	At least 1 of the following features: staphyloma, lacquer cracks, Fuchs' spot, or chorioretinal atrophy	Vongphanit et al. (2002)	Fundus photographs
b	M0, normal appearing posterior pole; M1, tessellation and choroidal pallor pattern; M2, posterior staphyloma; M3, lacquer cracks; M4, choroidal atrophy; M5, geographic atrophy and CNV	Avila et al. (1984)	Fundus photographs
c	1: tessellated fundus, 2; diffuse chorioretinal atrophy, 3: patchy chorioretinal atrophy, 4: macular atrophy, and 'plus' lesions: lacquer cracks, myopic CNV and/or Fuchs spot. MMD was defined as ≥2.	Ohno-Matsui et al. (2015)	Fundus photographs
d	At least 1 of the following features: diffuse chorioretinal atrophy at the posterior pole, patchy chorioretinal atrophy, lacquer cracks, or macular atrophy	Hayashi et al. (2010)	Fundus photographs

Table S3. Prevalence of Myopic Macular Degeneration in high myopia studies

Author	Country	Ethnicity	Age, years*	SER (D)*	MMD	MMD definition (Table S1)
Chen et al. (2012)	China	Chinese	40.6±17.1 (8-88)	-11.4±4.8	64.0%	c (≥2 excluding tessellation)
Lai et al. (2008)	Hong Kong	Chinese	36.0±12.2 (>18)	-10.2 ±4.0	11.3%	a (excluding tessellation)
Chang et al. (2013)	Singapore	Chinese, Malay and Indian	- (>39)	-	90.0%	b (≥M1; including tessellation)
Koh et al. (2016)	Singapore	Chinese	21.1±1.2 (19-25)	-8.9±2.1	8.3%	c (≥2 excluding tessellation)
Xiao et al. (2018)	China	Chinese	18.5 (7-70)	- 8.9 (-11.50, -7.63) †	43.0%	c (≥2 excluding tessellation)
Zhao et al. (2018)	China	Chinese	47.5±14.6 (>18)	-14.4±5.2	54.5%	c (≥2 excluding tessellation)

** Mean±standard deviation (range); SER = spherical equivalent of refraction; D = diopter; MMD = myopic macular degeneration. † 25th percentile, 75th percentile*

Table S4. Best corrected visual acuity (LogMAR) in eyes with and without myopic macular degeneration

Author	Country	Age, years (mean)	BCVA with MMD (mean)	BCVA without MMD (mean)	P-value
Vongphanit et al. (2002)	Australia	48.5	0.3	0.1	<0.001
Liu et al. (2010)	China	56.9	0.25	0.06	<0.001
Gao et al. (2011)	Rural China	51.9	0.3	0.1	<0.001
Chen et al. 2012)	Taiwan	72.2	0.72	0.27	0.001
Jonas et al. (2017)	Rural India	49.0	1.38	0.11	<0.001
Shih et al. (2006)	Taiwan	56.1	0.94	0.33	0.007
Lichtwitz et al. (2016)	France	60.0	0.74	0.25	<0.001
Zhao et al. (2018)	China	47.5	0.62	0.17	<0.001

BCVA = best corrected visual acuity, measured in logMAR

Table S5. Characteristics of the studies investigating the relationship between retinal detachment and cataract extraction

Study	Study type	Follow up time (months)	Type of CE	Total participants (number of myopes)	RD in myopes (%)	RD in emmetropes (%)	OR (95%CI)	Age, years*	Refractive error / axial length (D/ mm) *
Jeon et al. 2011	Case control study	7.27±±2.16	phaco	694†(347)	6 (1.7)	1 (0.28)	6.1 (0.7-50.8)	53.5±11.8	28.69±1.94 (case) 23.06±±2.17 (control)
Tsai et al. 2008	Case series	5.1-10.8	ECCE with IOL, phaco met IOL	52 (52)	2 (3.84)	-	-	61.3±13.2	28.22±1.64
Ku et al. 2002	Case series	6 - 82	ECCE with IOL, phaco met IOL	125 (125)	2 (1.60)	-	-	61.58±12.27	28.45±±3.41 (ECCE) 28.45±±3.03 (phaco)
Fan et al. 1999	Case series	12 -89	ECCE with IOL, phaco met IOL	118 (118)	2 (1.69)	-	-	59.8±13.8	30.13±±2.08
Alldredge et al. 1998	Retrospective case series	9- 77	phaco	80 (80)	0	-	-	61.0 (33-85)	-10.0D (-7.0D to -18.4D)
Gross et al. 1987	Retrospective case series	±±3-36	ECCE with IOL	117 (117)	1 (0.85)	-	-	69.2	-10.0D±1.08
Ripandelli et al. 2003	Retrospective, paired-eye, case–control trial.	36 months	ECCE	1860 * (930)	74 (7.96)	11 (1.18)	7.2 (3.8-13.7*)	62.5±8.5	-20.7D±4.2 (ECCE) -21.0D±3.8 (control)

** Mean±standard deviation (range); †emmetropes as control group; ‡myopes without cataract extraction as controls; CE = cataract extraction; ECCE = extracapsular cataract extraction; RD = retinal detachment; D = diopter; mm = millimeters*

Table S6. Characteristics of the studies investigating the relationship between myopia and open angle glaucoma progression

Authors	Study type	Country	Total number of participants (number of myopes)	Male Gender (%)	Age (years)*	SER myopes (D)*	SER non-myopes (D)*	Follow-up, years*	Measurement modality of VF
Ohno-Matsui et al. (2011)	Retrospective, observational series	Japanese	492 (492)	41.5	40.6±16.6	-13.4 (4.1)	-	10.2±3.4	Goldmann kinetic perimetry
Perdicchi et al. (2007)	Retrospective study	Italian	294 (264)	47.3	56.7±12.8	NA (+1.75 to >-3D)	+8 to +2	- (2-5.3)	Octopus 30° central field
Lee et al. (2008)	Retrospective study	Taiwan	176 (176) 76	48.1	48.6±14.2	NA (-3D to <-9D)	-	8.7±2.2	Humphrey perimeter, 30-2 SITA standard program
Doshi et al. (2007)	Retrospective case series	Chinese	14 (14)	100	38.9 (25-66)	≤-6	-	9.8±2.7	Static automated white on white threshold perimetry (SITA standard)
Chul Han et al. (2016)	Retrospective comparative longitudinal cohort study	Korean	232 (150)		45.7±11.8	-4.5 (2.7)	-1.2 (2.3)	9.9±2.6	Humphrey Field Analyzer
Yoshino et al. (2016)	Retrospective matched case control study	Japanese	140 (70)	56.6	48.8±10.2	-9.77 (2.50)	-1.62 (2.37)	9.48±4.18	Humphrey Field Analyzer
Park et al. (2016)	prospective observational study	Korean	179 (101)	45.8	70.2±15.8	-3.8 (3.46)	0.1±1.26	6.4±1.0	Humphrey VF examination
Lee et al. (2015)	Retrospective cohort study	Korean	369 (191) 151	52.0	61.4±12.1	-1.77 (1.45) to -9.21 (3.57)	0.71±1.04	4.4	Humphrey Field Analyzer

**mean±standard deviation (range); SER = spherical equivalent of refraction; VF = Visual Field; D = diopters*

Part III

Myopia prevalence from early childhood to adulthood

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2020 As the year of quarantine myopia

Caroline C.W. Klaver, Jan Roelof Polling, **Clair A. Enthoven**

JAMA ophthalmology
2021, 139(3), 300-301

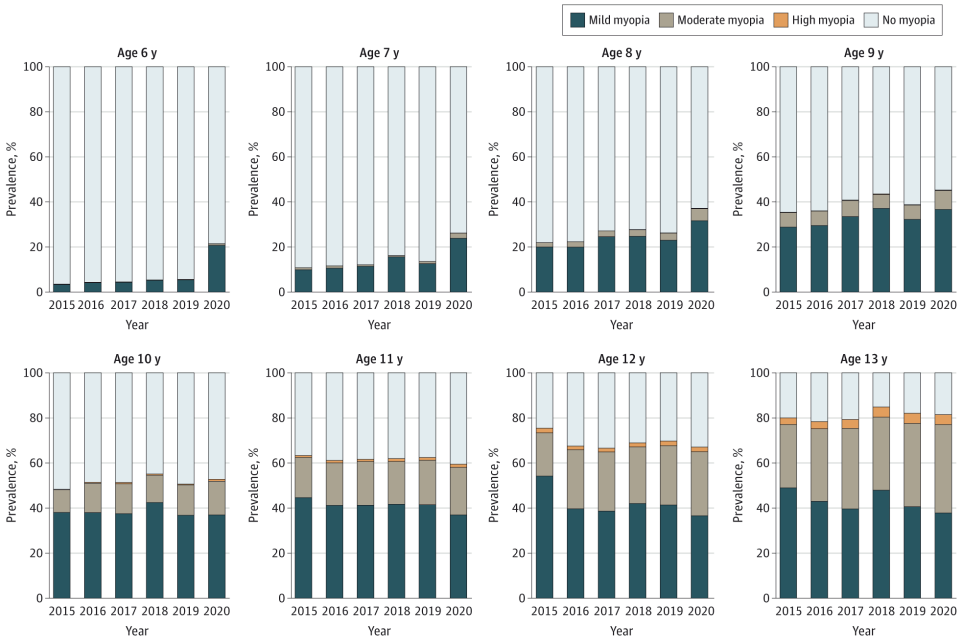
Although reports on coronavirus disease 2019 (COVID-19) affecting health already exceed 32 000 articles, studies on direct effects on the eye appear to be limited.[1] Conjunctivitis, retinitis, episcleritis, and optic neuritis have all been described as ocular manifestations, but frequency and morbidity are fortunately not striking. This has relieved us as ophthalmologists and given the impression that we have been spared a heavy patient load attributable to COVID-19 complications. We have focused on reorganizing our clinics and made sure that anti–vascular endothelial growth factor treatments and other urgent patient care were not obstructed.

In this issue of *JAMA Ophthalmology*, Wang et al[2] are telling us another story. They suggest we should be worried about the ophthalmic outcome of COVID-19, not from the virus itself but from the potential outcome of an antivirus measure on eye health, specifically an outcome in children that may have major consequences for visual acuity later in life. China, followed by other Asian countries, was the first to experience the severe virus outbreak, the first to start closing schools and imposing home confinement, and the first (to our knowledge) to report the potential consequences of these actions on myopia. For the eye, this appears to be development of myopia at a young age; particularly, an early onset potentially increases the burden.

What Wang et al[2] are reporting reflects an impressive scientific achievement. In China, a complete lockdown with home confinement took place from January to May, and schools reopened in June. During this 1 month, the examiners performed noncycloplegic photorefraction in schoolchildren aged 6 to 13 years; during the 3 months that followed, they analyzed all data and prepared for publication. The study was part of a yearly survey that started in 2015 and was in its totality truly big data (N = 123 535). A slight but potentially relevant omission is the number of children who participated each year, particularly this year. It is therefore unclear whether the number of participants in 2020 is the same as in other years, which would provide greater confidence of a fair comparison. Also, cycloplegic refractions are the gold standard in defining myopia in this age group.

To assess temporal trends across age groups, the authors[2] calculated the mean spherical equivalent for each age at each year and estimated the prevalence of myopia. Overall, it is important to note the high proportion of myopia in these Asian children who are still in elementary school. At age 13 years, more than 80% already had myopia, while the prevalence at this age in European children is 25%. At all ages, mean refractive error involved greatest myopia in 2020, in girls even more so than boys. Most compelling, however, were the data in 6-year-old children. Their mean refractive error changed only slightly from the hyperopic side of 0 in 2019 to the myopic side this year. Nevertheless, this myopic shift had a large association on the prevalence of myopia (SE <–0.5D), as it jumped from 3.5% to 5.7% in 2015 to 2019 to 21.5%, an almost 400% increase, in 2020. For 7-year-old and 8 year-old participants, this increase was also considerable: 200% and 40%, respectively. At older ages, the 2020 surplus

was not apparent, but at these ages, the total myopia prevalence was already substantial in the years prior to 2020 (Figure 1). Taken together, the prevalence data after the COVID-19 lockdown in China suggest an earlier onset for a large proportion of children. This age shift is highly clinically relevant, in that it is well recognized that age at onset corresponds closely to final refractive error at adult ages. Likewise, the higher the refractive error, the more likely the occurrence of sight-threatening complications, such as myopic retinal degeneration, glaucoma, and retinal detachment. Given that 1 in 3 people with high myopia becomes severely visually impaired, mostly at working age, it is clear that China is facing a serious public health problem. Much of the rest of the world may be likely to follow.



Prevalence of Refractive Error for Primary School Students Aged 6 to 13 Years During the 6 Years of Screenings. The prevalence of mild myopia increased in 2020 compared with previous years in children aged 6 to 8 years. Mild myopia: −3 diopters (D)<spherical equivalent refraction (SER)≤−0.5 D; moderate myopia: −6 D<SER≤−3 D; high myopia: SER≤−6 D; and no myopia: SER>−0.5 D. From Wang et al (2021) *JAMA Ophthalmology*.[2]

Quarantine home confinements happened all over the world in the first 5 months of 2020. Some countries did not allow leaving the house at all; others were more lenient. A number of studies reported on lifestyle during this time. A Canadian study assessed physical activity, outdoor time, screen time, and social media use in children by questionnaire during the lockdown.[3] Eight-year-olds spent a mean of 5.14 h/d on screens for leisure, and 83.5% consumed more than the

recommended screen time limit of 2 h/d. Parents reported a decrease in healthy behavior, most dramatically for outdoor activity and sport. This study also showed a sex difference: girls spent more time on screens and social media and less time on physical activity. Other studies at other parts in the world published similar reports on increased screen time and decreased outdoor play by children during strict COVID-19 regulations.[4-6] The observation that COVID-19 induces lifestyle changes, as well as an increase in myopia prevalence, makes a strong case that these 2 pandemics are linked and fit the current understanding of myopiagenesis.

Why did Wang and coauthors[2] only find relevance for the 2020 myopia increase in 6-year-old to 8-year-old children? The older age groups were also home confined, with even more online education. We speculate 2 reasons. First, young children may be more sensitive to myopic triggers from the environment. Such age effects have also been found in the Sydney Adolescent Vascular and Eye Study.[7] In this study, children who developed myopia spent 1.5 hours more on near work than children without myopia, but this was only in the younger cohort of 6-year-old participants and not in the older cohort of 12-year-old participants.[7] The sensitivity may have a statistical origin. Growth curves of axial length (http://www.myopie.nl) and refractive error charts are much steeper at ages 6 to 9 years than older ages, demanding less power to find statistically significant associations. Secondly, older age groups spent less time outdoors and increased time on near-work activities even before the national lockdown. Their behavioral exposure was already abundant. Of course, we cannot rule out chance from this single study.[2]

In conclusion, 2020 will be a memorable year for many reasons. The quarantine measures were and still are important and our best bet to reduce the spread of the virus. Nevertheless, an intelligent lockdown might need to consider careful planning of indoor activities and preferably not restrict outdoor play in young children. That may help control a wave of quarantine myopia.

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Part IV

Lifestyle factors and myopia development

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The impact of computer use on myopia development in childhood: the Generation R study

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ABSTRACT

Environmental factors are important in the development of myopia. There is still limited evidence as to whether computer use is a risk factor. The aim of this study is to investigate the association between computer use and myopia in the context of other near work activities. Within the birth cohort study Generation R, we studied 5074 children born in Rotterdam between 2002 and 2006. Refractive error and axial length was measured at ages 6 and 9. Information on computer use and outdoor exposure was obtained at age 3, 6 and 9 years using a questionnaire, and reading time and reading distance were assessed at age 9 years. Myopia prevalence (spherical equivalent ≤-0.5 diopter) was 11.5% at 9 years. Mean computer use was associated with myopia at age 9 (OR=1.005, 95% CI=1.001-1.009), as was reading time and reading distance (OR=1.031; 95% CI=1.007-1.055 (5-10 hr/wk); OR=1.113; 95% CI=1.073-1.155 (>10 hr/wk) and OR=1.072; 95% CI=1.048-1.097 respectively). The combined effect of near work (computer use, reading time and reading distance) showed an increased odd ratio for myopia at age 9 (OR=1.072; 95% CI=1.047-1.098), while outdoor exposure showed a decreased odd ratio (OR=0.996; 95% CI=0.994-0.999) and the interaction term was significant (P=0.036). From our results, we can conclude that within our sample of children, increased computer use is associated with myopia development. The effect of combined near work was decreased by outdoor exposure. The risks of digital devices on myopia and the protection by outdoor exposure should become widely known. Public campaigns are warranted.

INTRODUCTION

Myopia, or near-sightedness, is a refractive error of the eye that can be corrected by glasses or contact lenses. It is primarily caused by an excessive elongation of the eyeball resulting in thinning of all retinal layers. In particular, high degrees of myopia (-6 diopters or worse), is associated with retinal complications causing irreversible visual impairment later in life[1]. The prevalence of myopia has increased rapidly in the last decades. Over 80% of the university students in highly urbanized areas in East Asia are currently myopic; Europe is following with 50% of the young adults developing myopia.[2-4]

Known risk factors for myopia are lifestyle factors including lack of outdoor exposure, near work duration and near working distances.[5, 6] Concerns or awareness of digital devices on children's health is increasing.[7-9] The exact contribution of digital screens to the total time spent on near work by children is unknown, but a recent study showed that children aged 0 to 8 years spent on average more than one hour per day on a computer, tablet or smartphone.[10] However, there is still limited evidence of whether computer use is a risk factor for myopia.[11] Cross-sectional studies showed conflicting results and evidence from longitudinal studies is scarce.[11, 12] We analyzed data from the prospective birth cohort the Generation R study, where computer use was measured at the age of 3, 6 and 9 years. Our first aim was to determine the association between computer use and myopia and axial elongation. Our second aim was to relate the effect of computer use to other near work activities associated with myopia and axial elongation. The third aim was to investigate whether the effect of near work can be modified by outdoor exposure.

METHODS

Study population

Generation R is a population-based prospective birth cohort of 9,778 pregnant women and their children who were born between April 2002 and January 2006 in Rotterdam, The Netherlands. Details of the methodology of this study has been described elsewhere.[13, 14] Of the initial cohort, 5,431 (55.5%) children visited the research center at both the age of 6 and 9 years. Children with computer use measurements of at least one time point (age 3, 6 or 9) were included in the study (N=5,076). Only 2 out of 5,076 children did not have any eye measurements and were therefore excluded, leaving 5,074 children available for analyses (Figure 1). The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam (MEC 217.595/2002/20), and written informed consent was obtained from all parents.

Eye measurements

At both 6 and 9 years, visual acuity was measured with LEA charts at a 3-m distance by means of the Early Treatment Diabetic Retinopathy Study method.[15] In children with visual acuity of more than 0.1 logarithm of the minimum angle of resolution (LogMAR) in at least 1 eye, or in children with an ophthalmologic history automated cycloplegic refractive error was performed using a Topcon KR8900 instrument (Topcon, Japan). Those with visual acuity of 0.1 LogMAR or less, no glasses, and no ophthalmic history were classified as non-myopic.[16, 17] Two drops (three in case of dark irises) of cyclopentolate (1%) with 5 minutes interval were dispensed, and refractive error measurements were performed at least 30 minutes thereafter when pupil diameter was ≥6 mm. Automated cycloplegic refractive error measurement regardless of visual acuity was introduced for all children during the research phase at 9 years. Myopia was defined as spherical equivalent (SER) ≤-0.5 diopter in at least one eye. Ocular biometry was measured by Zeiss IOL-master 500 (Carl Zeiss MEDITEC IOL-master, Jena, Germany). For axial length (AL), five measurements per eye were averaged to mean AL. Axial elongation was calculated in millimeters per year by taking the difference between AL at age 6 and 9 divided by the time in years between measurements. Mean axial elongation of two eyes was used in the analyses.

Computer use, outdoor exposure, reading time and reading distance

Desktop computer use and outdoor exposure were measured at age 3, 6 and 9 years using a questionnaire filled out by the main caretaker. The question "how much time does your child use the computer in the morning/afternoon/evening" was asked for weekdays and weekend days separately. Total hours computer use per week was computed as the sum of 5 times weekdays and 2 times weekend days. The average amount of computer use was estimated by the sum of computer use at age 3, 6 and 9 divided by 3. Outdoor exposure was asked and processed similarly. Groups of low (<7.0 hr/wk), medium (7.0-14.0 hr/wk) and high (>14 hr/wk) outdoor exposure were created. Children with >40 hours computer use per week were set to 40 hours per week (N=15). Time spent reading was asked per week (<5 hr/wk, 5-10 hr/wk or >10 hr/wk), and reading distance was asked for <30 cm or ≥30 cm at age 9.

Potential confounders

Ethnic background was determined by questionnaire and children were classified into European or non-European. Other potential confounders were sex and age.

Statistical analyses

Myopia (yes/no) was considered the dichotomous outcome variable (N=5021 at 6 years, N=4706 at 9 years); Axial elongation (mm/year) was used as the continuous outcome (N=4511). Axial elongation was positively skewed, therefore log transformation was performed on this variable. Missing information on determinants and covariates varied between 0% and 35%

(Table 1). Multiple imputation procedures to replace missing covariates for the most likely values were performed using Multivariate Imputations by Chained Equations (MICE).[18] First, parallel logistic and linear regression models were performed with computer use as determinant, and myopia at 6 and 9 years, and axial elongation as outcomes, and the average amount of computer use over time with myopia at 9 years and axial elongation as the outcomes. Second, conditional analyses taking into account the correlation between computer use measurements over time were applied to identify the most important time period.[19] Z-scores of computer use were created and regressed on earlier computer use measures. We calculated two conditional computer use variables; computer use at age 6 condition on computer use at age 3 (6|3) and computer use at age 9 condition on computer use at age 6 and 9 (9|3 and 6), by saving the standardized residuals of the regression analyses. The conditional z-score is a measure of computer use change between two time points, and can be interpreted as computer use above or below the expected given earlier computer use.[20] Third, the strength of the associations of different types of near work activities on myopia at age 9 and axial elongation was determined. Computer use and reading time at age 9 were compared by creating similar cut-of values (<5 hr/wk, 5-10 hr/wk and >10 hr/wk). Univariate regression analyses were performed for computer use, reading time and reading distance on myopia at age 9 and axial elongation. Fourth, a weighted risk score was created by combining the effects of computer use, reading time, and reading distance. All three were standardized to avoid variables with larger ranges having a greater importance on the outcome. A multivariate, logistic regression on mean computer use, reading time and reading distance was built. The risk score was computed for each individual using the natural logarithm of the odds ratios of the final multivariate regression model multiplied by the standardized values of the near work variables. Logistic and linear regression analyses were performed to test for interactions with the near work risk score and outdoor exposure. P-values <0.05 were considered to be significant for interaction analyses. All analyses were performed with the full dataset (N=5074) minimizing selection bias. Sensitivity analyses were performed with complete computer use measurements (N=2745 in total, N=2716 for myopia at 6, N=2624 for myopia at 9, and N=2507 for axial elongation).

RESULTS

Half (50.1%) of the children were girls, and 70.2% were from European ethnicity. The mean age at eye measurements was 6.10 (0.44) and 9.78 (0.34) years (Table 1). Myopia prevalence was 2.2% at 6 years and 11.5% at 9 years. Axial length was 22.34 (0.74) mm at 6 years and 23.09 (0.84) mm at 9 years. Mean weekly computer use was 0.49 (1.79) hr/wk at the age of 3 years (N=3604), 2.19 (3.27) hr/wk at the age of 6 years (N=4413), and 5.17 (5.51) hr/wk at 9 years of age (N=4150; Table 1). Children from non-European ethnicity spent more time on a computer at age 3, 6 and 9, less time outdoors at age 3, 6 and 9, and less time reading at age 9.

Table 1. General characteristics

Generation R cohort (N=5074)	Age 3	Age 6	Age 9
Age (±SD; years)	3.05	6.10 (0.44)	9.78 (0.34)
Missing (%)	26.8	0	0
Sex (% ♀)	50.1	50.1	50.1
Missing (%)	0	0	0
Ethnicity (% EUR)	70.2	70.2	70.2
Missing (%)	0.6	0.6	0.6
Myopia (%)	-	2.2	11.5
Missing (%)	-	1.0	3.5
Axial length (±SD; mm)	-	22.34 (0.74)	23.09 (0.84)
Missing (%)	-	5.3	6.2
Axial elongation (±SD; mm/yr)	-	-	0.21 (0.08)
Missing (%)	-	-	11.1
Computer use (±SD; hr/week)	0.49 (1.79)	2.19 (3.27)	5.17 (5.51)
Missing (%)	29.0	13.0	18.2
Outdoor exposure (±SD; hr/week)	11.2 (5.85)	11.7 (7.90)	7.6 (5.23)
Low <7.0 hr/wk (%)	36.9	30.1	53.7
Medium 7.0-14.0 hr/wk (%)	37.6	38.5	32.0
High >14.0 hr/wk (%)	25.5	31.4	14.3
Missing (%)	29.6	24.9	15.3
Reading time	-	-	
<5 hr/wk (%)			62.2
5 – 10 hr/wk (%)			30.0
> 10 hr/wk (%)			7.8
Missing (%)			30.8
Reading distance (% <30 cm)	-	-	48.6
Missing (%)			35.0

Logistic regression analyses showed significant associations between computer use at 3 years and myopia at 6 and 9 years, (OR=1.005, 95% CI=1.001-1.010; OR=1.009, 95% CI=1.002-1.016), and borderline significant associations with computer use at 9 years and myopia at 9 years and axial elongation (OR=1.002, 95% CI=1.000-1.009; β=0.002 *P*=0.053). The cumulative time of computer use in childhood (mean computer use) was significantly associated with myopia at 9 years (OR=1.005, 95% CI=1.001-1.009), but not with axial elongation (Table 2). Sensitivity analyses on the complete dataset (N=2745) showed similar results, however, computer use at 3 years became insignificant with respect to myopia at 6 and 9 years, and computer use at 9 years and mean total computer use were significant with respect to myopia at 9 years (OR=1.005, 95% CI=1.001-1.010; OR=1.009, 95% CI=1.002-

1.016 respectively) and axial elongation (β=0.004 P=0.018; β=0.008 *P*=0.020 respectively) (Table S1). Effects were similar for Europeans and non-Europeans (data not shown); outdoor exposure did not correlate with computer use (Figure S2).

Table 2. Logistic regression analyses of computer use on myopia at 6 and 9 years and axial elongation

Myopia at 6 years; N=5021	**Odds Ratio**	**95% CI**		**P-value**
Computer use at 3 years	1.005	1.001	1.009	0.006
Computer use at 6 years	1.000	0.998	1.001	0.825
Myopia at 9 years; N=4706	**Odds Ratio**	**95% CI**		**P-value**
Computer use at 3 years	1.009	1.002	1.016	0.014
Computer use at 6 years	1.001	0.998	1.004	0.605
Computer use at 9 years	1.002	1.000	1.003	0.062
Mean computer use	1.005	1.001	1.009	0.015
Axial elongation; N=4511	**Estimate**	**SE**		**P-value**
Computer use at 3 years	0.008	0.004		0.065
Computer use at 6 years	-0.002	0.002		0.404
Computer use at 9 years	0.002	0.001		0.053
Mean computer use	0.004	0.002		0.099

Adjusted for age, sex, ethnicity; N= 5021 for myopia at age 6; N= 4706 for myopia at age 9; N= 4511 for axial elongation. Axial elongation was log transformed.

We performed conditional analyses to identify whether a particular age period was most important by adjusting for previous computer use. The strongest association was at 3 years in the full dataset (OR=1.017; 95% CI=1.003-1.031 for myopia; β=0.015, *P*=0.063 for axial elongation). However, conditional analyses on the complete dataset (N=2745) showed the strongest association for computer use at 9 years (OR=1.012; 95% CI=1.000-1.024 for myopia; β=0.018, *P*=0.029 for axial elongation) (Table S2 and S3). These discrepancies prompted us to perform all further analyses with mean computer use.

Reading time at age 9 was associated with myopia at age 9 as well as axial elongation (OR=1.031; 95% CI=1.007-1.055 and OR=1.113; 95% CI=1.073-1.155 for myopia; β=0.069; $P=2.32e^{-5}$ and β=0.151; $P=7.26e^{-9}$ for axial elongation), while computer use at age 9 was not significantly associated when using similar cut-off values for both variables (Table 3). Reading distance was associated with myopia at age 9, but not with axial elongation (OR=1.072; 95% CI=1.048-1.097 for myopia; β=0.021; *P*=0.128 for axial elongation; Table 3). Excluding hyperopic children (SER ≥+2D) from the axial elongation analysis (N=384) resulted in a significant association with reading distance (β=0.038, *P*=0.038; data not shown).

Table 3. Logistic and linear univariate regression analyses of computer use, reading time, and reading distance on myopia at 9 years and axial elongation

Myopia at 9 years; N=4706	**Odds Ratio**	**95% CI**		**P-value**
Computer use at 9 years				
< 5 hr/wk	Ref			
5-10 hr/wk	1.004	0.982	1.027	0.695
> 10 hr/wk	1.009	0.981	1.037	0.540
Reading time at 9 years				
< 5 hr/wk	Ref			
5-10 hr/wk	1.031	1.007	1.055	0.011
> 10 hr/wk	1.113	1.073	1.155	$1.54e^{-8}$
Reading distance				
>30cm	1.072	1.048	1.097	$1.30e^{-9}$
Axial elongation; N=4511	**Estimate**	**SE**		**P-value**
Computer use at 9 years				
< 5 hr/wk	Ref			
5-10 hr/wk	0.008	0.015		0.607
> 10 hr/wk	0.034	0.019		0.078
Reading time at 9 years				
< 5 hr/wk	Ref			
5-10 hr/wk	0.069	0.016		$2.32e^{-5}$
> 10 hr/wk	0.151	0.026		$7.26e^{-9}$
Reading distance				
>30cm	0.029	0.019		0.128

Adjusted for age, sex and ethnicity; N=4706 for myopia at age 9; N=4511 for axial elongation. Axial elongation was log transformed.

Near work risk scores were calculated by weighting mean computer use, reading time, and reading distance (Table S4). The near work risk score and mean outdoor exposure were associated with myopia at age 9 and axial elongation, as was the interaction term for myopia at 9 (*P* for interaction=0.036). The effect of near work activities decreased within higher levels of outdoor exposure (Table 4; Figure 1).

Table 4. Linear and logistic regression analyses of the near work risk score and mean outdoor exposure including interaction on myopia at 9 years and on axial elongation

Myopia at 9 years; N=4706	**Odds Ratio**	**95% CI**		**P-value**
Near work risk score	1.072	1.047	1.098	$8.30e^{-9}$
Mean outdoor exposure	0.996	0.994	0.999	0.001
Near work risk score * Mean outdoor exposure	0.998	0.995	1.000	0.036
Axial elongation; N=4511	**Estimate**	**SE**		**P-value**
Near work risk score	0.059	0.018		0.001
Mean outdoor exposure	-0.004	0.002		0.004
Near work risk score * Mean outdoor exposure	-0.002	0.002		0.259

Adjusted for age, sex and ethnicity; N= 4706 for myopia at age 9; N= 4511 for axial elongation. Axial elongation was log transformed.

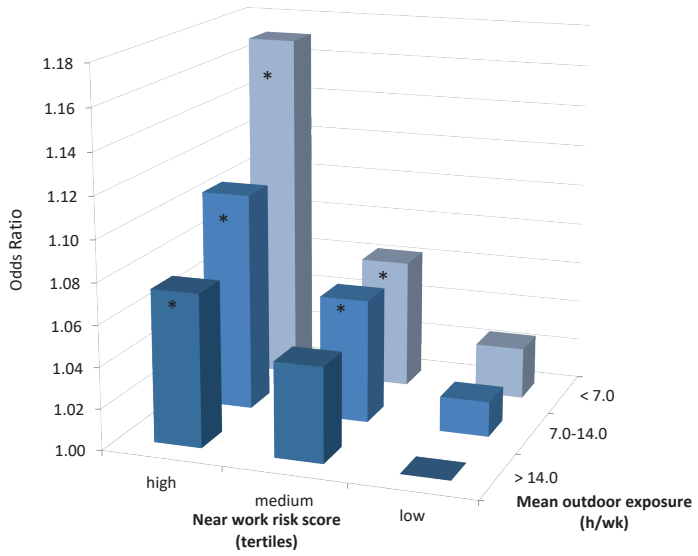

Figure 1. Odds Ratios for near work risk tertiles and mean outdoor exposure on myopia at age 9

DISCUSSION

In our study cohort consisting of 5074 children from the Generation R study, we found that computer use in young children was moderately associated with myopia. Reading time had a stronger association, suggesting that prolonged hours of reading books may result in a higher risk of myopia than desktop computer screens. Notably, the effect of combined near work activities could be diminished by outdoor exposure.

Whether computer use is a risk factor for myopia has been questioned for a long time.[21] Although this topic has been studied extensively, most studies were cross-sectional and results were inconclusive.[6, 22-25] In our longitudinal study, computer use already at age 3 years was associated with myopia occurring at school age. Few other longitudinal studies have been performed on this topic; two of them reported an association between computer use and myopia progression.[26, 27] Both studies were performed in young adults after the development of myopia, jeopardizing the conclusion of a causal relation.

Given the evidence from a recent meta-analysis on observational studies, total near work was recognized as a risk factor for myopia, despite the lack of randomized controlled trials.[5] This study underlines the consequences of near work activities in childhood. In our study, we confirmed that reading time and reading distance were associated with myopia and axial elongation.[6, 27-29] In relation to reading habits, the effect of computer use appeared somewhat less strong, which may relate to the fact that reading books involves a closer reading distance than using a desktop computer.

A causal association between outdoor exposure in childhood and myopia incidence and progression has been well established by multiple randomized controlled trials.[30-32] The results of our study suggest that the hours of outdoor exposure needed to prevent children from myopia depends on the intensity of near work activities. Results were in line with findings from Rose et al. (2008), who reported that the effect of near work may be modified by outdoor exposure.[33, 34] A longitudinal study observed that a minimal of 12 hr/wk outdoor exposure in childhood was needed to remain non-myopic.[35] The results of our study suggested that more than 7 hr/wk is needed to compensate low intensity near work, and more than 14 hr/wk for protection against medium or high intensity near work.

Even though the effect sizes identified in our study are relatively small, our results may have a large impact on a population scale. A recently published paper on sedentary behavior among the US population showed that computer use >1 hr/day has increased from 43% in 2001-

2002 to 56% in 2015-2016 in young children.[36] The use of handheld digital devices was not taken into account, and it is likely that they have an even greater effect on myopia because of their shorter reading distance than computers.

A strength of this study is the longitudinal design; computer use was measured at three different time points and eye measurements were performed at two different time points. We were therefore able to identify the association with early onset myopia and myopia progression by using axial elongation. This study also benefitted from a large sample size and the young age of the children. Nevertheless, some limitations should be borne in mind. Around 45% of the study cohort had missing information on computer use at 1 (31.6%) or 2 (14.3%) time points. Children with missing information did not differ in sex, outdoor exposure, reading time, or reading distance, but were more often non-European (50.1% versus 18.5%; P<0.001). Therefore, we performed multiple imputation procedures to include these children in the main analyses. Sensitivity analyses on the complete dataset showed similar results indicating no large bias. Unfortunately, potential risk factors were assessed by questionnaires filled out by parents which could have resulted in socially desired answers. This may explain our inconsistent findings for computer use at the different time points. Automated measurements are currently under development, and may provide more objective digital exposures.

CONCLUSION

Our results showed that computer use, especially at a very young age, is associated with myopia development in childhood. Reading time had a stronger association with myopia, possibly because of a shorter near work distance. The effect of combined near work activities could be lowered by outdoor exposure. It is likely that the increased use of digital devices may have a large impact on myopia development in the coming years. Therefore, regulating its use, and maximizing outdoor exposure in young children should be the main focus for myopia prevention.

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SUPPLEMENTS

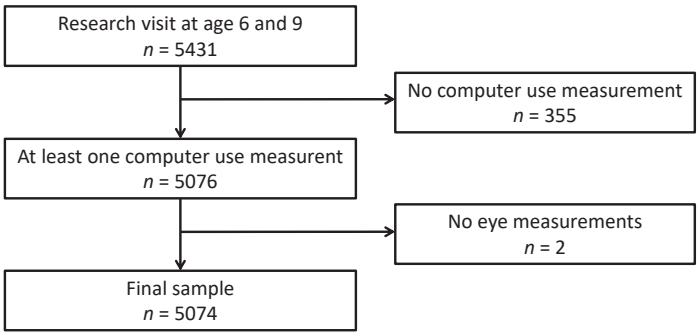

Figure S1. Flowchart of study population

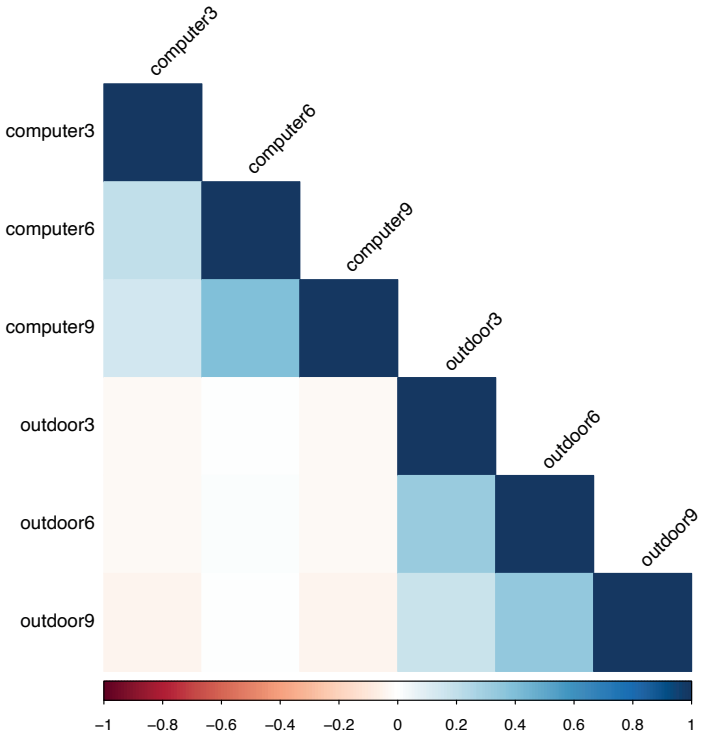

Figure S2. Correlation matrix of computer use (hr/wk) at age 3, 6 and 9 (computer3, computer6 and computer 9) and outdoor exposure (hr/wk) at age 3, 6 and 9 (outdoor3, outdoor6 and outdoor9)

Table S1. Sensitivity analyses of logistic regression analyses of computer use on myopia and axial elongation

Myopia at 6 years; N=2716	**Odds Ratio**	**95% CI**		**P-value**
Computer use at 3 years	1.003	1.000	1.006	0.062
Computer use at 6 years	1.000	0.998	1.002	0.677
Myopia at 9 years; N=2624	**Odds Ratio**	**95% CI**		**P-value**
Computer use at 3 years	1.006	0.999	1.013	0.099
Computer use at 6 years	1.004	0.999	1.008	0.127
Computer use at 9 years	1.003	1.001	1.005	0.015
Mean computer use	1.007	1.002	1.013	0.005
Axial elongation; N=2507	**Estimate**	**SE**		**P-value**
Computer use at 3 years	0.007	0.005		0.152
Computer use at 6 years	0.002	0.003		0.540
Computer use at 9 years	0.004	0.002		0.018
Mean computer use	0.008	0.004		0.020

Adjusted for age, sex, ethnicity; N= 2716 for myopia at age 6; N=2624 for myopia at age 9 and N=2507 for axial elongation. Axial elongation was log transformed.

Table S2. Multivariate conditional regression analyses of computer use on myopia at age 9 and axial elongation

Myopia at 9 years; N=4706	**Odds Ratio**	**95% CI**		**P-value**
Computer use at 3 years	1.017	1.003	1.031	0.015
Computer use at 6 years	1.006	0.996	1.015	0.251
Computer use at 9 years	1.006	0.996	1.015	0.237
Axial elongation; N=4511	**Estimate**	**SE**		**P-value**
Computer use at 3 years	0.015	0.008		0.063
Computer use at 6 years	-0.013	0.007		0.056
Computer use at 9 years	0.015	0.006		0.016

Adjusted for age, sex and ethnicity; N=4706 for myopia at age 9; N=4511 for axial elongation. Axial elongation was log transformed.

Table S3. Sensitivity analyses of multivariate conditional regression analyses of computer use on myopia at age 9 and axial elongation

Myopia at 9 years; N=2624	**Odds Ratio**	**95% CI**		**P-value**
Computer use at 3 years	1.010	0.998	1.021	0.090
Computer use at 6 years	1.008	0.996	1.019	0.183
Computer use at 9 years	1.012	1.000	1.024	0.049
Axial elongation; N=2507	**Estimate**	**SE**		**P-value**
Computer use at 3 years	0.011	0.008		0.144
Computer use at 6 years	0.003	0.008		0.670
Computer use at 9 years	0.018	0.008		0.029

Adjusted for age, sex and ethnicity; N=2624 for myopia at 9; N=2507 for axial elongation. Axial elongation was log transformed.

Table S4. Multivariate regression analyses of near work activities on myopia and axial elongation for the calculation of the near work risk score

Myopia at 9 years; N=4706	**ln(Odds Ratio)**	**SE**	**P-value**
Mean computer use	0.017	0.006	0.002
Reading time at age 9	0.028	0.005	3.03^{e}-8
Reading distance at age 9	0.035	0.006	1.30^{e}-9

Adjusted for age, sex and ethnicity; N= 4706. Mean computer use, reading time and reading distance were standardized.

7

Smartphone use associated with refractive error in teenagers; the Myopia app Study

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ABSTRACT

Purpose: To investigate the association between smartphone use and axial length and refractive error in teenagers using the Myopia app.

Design: Cross-sectional population-based study.

Participants: A total of 525 teenagers aged 12 to 16 year old from six secondary schools and from the birth cohort study Generation R participated in this study.

Methods: A smartphone application (Myopia app) was designed to objectively measure smartphone use and face to screen distance, and to pose questions about outdoor exposure at regular intervals. Participants underwent cycloplegic refractive error and ocular biometry measurements. Mean daily smartphone use was calculated in hours per day; continuous use in the number of episodes of 20 minutes on screen without breaks. Linear mixed models were conducted with smartphone use, continuous use, and face to screen distance as determinants, and spherical equivalent (SER) and the ratio of axial length and corneal radius (AL/CR) as outcome measures stratified by median outdoor exposure.

Main outcome measures: SER in diopters and AL/CR ratio.

Results: The teenagers were on average 13.7 (0.85) years old, 54% of them were girls. Myopia prevalence was 18.9%. During schooldays, total smartphone use was on average 3.71 (1.70) hr/day, and was only borderline significantly associated with AL/CR (β=0.008, 95%CI=-0.001, 0.017) and not with SER. Continuous use was on average 6.42 (4.36) episodes of 20 minutes use without breaks/day, and was significantly associated with SER and AL/CR (β=-0.07, 95%CI=-0.13, -0.01; β=0.004, 95%CI=0.001-0.008, respectively). When stratifying for outdoor exposure, continuous use remained only significant for teenagers with low exposure (β=-0.10, 95%CI=-0.20, -0.01 and β=0.007, 95%CI=0.001-0.013 for SER and AL/CR, respectively). Smartphone use during weekends was not significantly associated with SER and AL/CR, nor was face to screen distance.

Conclusions: Dutch teenagers spent almost 4 hours per day on their smartphones. Episodes of 20 minutes continuous use was associated with more myopic refractive errors particularly in those with low outdoor exposure. This study suggests that frequent breaks should become a recommendation for smartphone use in teenagers. Future large longitudinal studies will allow more detailed information on safe screen use in youth.

INTRODUCTION

Myopia is a refractive error caused by disproportionate eye growth during childhood and adolescence.[1] The prevalence of myopia is rising all over the world.[2,3] Currently, almost 50% of the young adults in Europe and 80-90% of the young adults in urban areas of East Asia are myopic.[2,4,5] An early onset of myopia results in higher degrees of myopia in adulthood.[6,7] This can lead to visual impairment and even blindness due to retinal complications later in life.[8,9] The rise in myopia prevalence in the last decade is caused by many lifestyle and behavioral changes.[10] For instance, spending less time outdoors is an established risk factor; the role of prolonged near work is still debated but many reports conclude an association.[11-13] These environmental factors may also explain that children growing up in urban areas are more often myopic than those growing up in rural areas.[14-16]

In the last years, researchers have speculated that smartphone use is an additional risk factor for myopia. Time spent on smartphones adds considerably to the total hours spent on near work among teenagers.[17] On the other hand, the 'myopia boom' started in 1950,[18] when smartphones did not yet exist. Smartphones are relatively new, and children growing up with smartphones are yet to become adults. Long term effects, including the influence on the myopia prevalence, are yet to be determined. Smartphone use is prone to underreporting and therefore difficult to determine by questionnaire.[19] For the current study, we developed a smartphone application (the Myopia app) that registers smartphone use and face-to-screen distance electronically to allow for objective measurements. We assessed the association between smartphone use, outdoor exposure and refractive error as measured by the Myopia app and self-reported outdoor exposure. We hypothesized that increased smartphone use is associated with a more myopic refractive error, and this association may be modified by outdoor exposure.

METHODS

Study populations: Myopia App Study (MAS) and Generation R

Teenagers aged 12 to 16 years old from two cohorts were eligible to enroll in the study; participants of the Myopia App Study (MAS), and the Generation R study. The MAS participants were recruited from six secondary schools in semi-urban areas in the Netherlands. Schools were asked to disseminate information on MAS among their pupils, and 300 teenagers from the first, second, and third grade (ages 12 to 16 years) consented to participate (Figure S1). Generation R is a large, prospective population-based birth-cohort in which 9778 pregnant mothers were enrolled between 2002 and 2006. Details of the methodology of this study has

been described elsewhere.[20,21] Of the initial cohort, 4929 (50%) children visited the research center at age 13 years. The app measurements were introduced during the final part of the study phase in April 2019 and 225 teenagers signed informed consent (Figure S1).

The app and ophthalmic measurements were performed between November 2018 until December 2019 in both cohorts. Two participants did not undergo eye measurements; 361 participants installed the app. Valid smartphone and eye measurements were available for 272 participants, as 25% of participants did not allow the app to run in the background of the operating system or technical issues hampered registration (Figure S1). Written informed consent from both parents and the teenagers was obtained before eye examination and app measurements. The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam (MEC-2018-005, NL63977.078.17 Myopia App Study and MEC-217.595/2002/20, Generation R study). The study project was conducted according to the Declaration of Helsinki.

Mobile application

The Myopia app was developed by the company Innovattic (www.innovattic.com), and was made available for the smartphone operation systems iOS and Android. This smartphone logging app registered smartphone use, and face to screen distance (see below). The teenagers received questions about outdoor exposure twice a week through pop up notifications in the app. In order to encourage the teenagers to answer all questions, gamification techniques were implemented in the app, i.e. different 'levels' were used to perform the measurements. Participants were rewarded with extra points once a questionnaire was completed; and an avatar received new 'gadgets' (i.e. hat or sunglasses) with increasing number of points. After five weeks, the teenagers were rewarded an online shopping voucher with a value corresponding to the amount of questions answered (up to €7.50).

Smartphone use

Smartphone use was measured during five weeks. The time of locking and unlocking the smartphone was registered using Unix timestamps, and participants were advised not to close the app. In that way, the app continued running in the background, which was needed as the closed operating systems of iOS and Android hampered continuous registration. We took particular care to identify measurement errors that occurred when participants (unintentionally) closed the app. Depending whether the last measurement was registered as 'screen off' or 'screen on' before the app stopped running in the background, this resulted in days with very low smartphone or extremely long continuous use. Days with less than 5 minutes of smartphone use in total, or days with more than 5 hours continuous use without locking the screen were excluded (on average 7.9 days per participant, or 33.9%), resulting in an average of 19.7 (SD 14.5; median 17.0; IQR 23) measurement days per participant. In order

to check for bias due to measurement error, we also excluded days with less than 1 minute of smartphone use in total, or days with more than 4 hours continuous use (on average 8.7 days per participant, or 35.7%), resulting in an average of 19.0 (SD 14.0; median 17.0; IQR 21.0) measurement days per participant, and days with less than 10 minutes of smartphone use in total. Excluding days with more than 6 hours continuous use (on average 7.4 days per participant, or 32.1%) resulted in an average of 20.3 (SD 14.7; median 18.0; IQR 22.0) measurement days per participant. The main analyses were performed using the first data processing manner (excluding days <5 min in total and >5 hours continuous use). Sensitivity analyses were performed using the second (more strict) and third (less strict) data processing manner (excluding days <1 min in total and >4 hours continuous use; and excluding days <10 min in total and >6 hours continuous use) to ensure the association between smartphone use and refractive error was not driven by our choice of excluding measurement days.

Smartphone use (hr/day) was calculated by summing the total time of smartphone use divided by the number of days the app was running. Continuous smartphone use was calculated by the sum of screen times ≥20 minutes divided by 20. For example, a participant had 5, 53, 22, 19 and 68 minutes of smartphone use on one day, continuous use was calculated by summing 53, 22 and 68 (143 minutes) divided by 20, i.e. 7.15 episodes of 20 minutes continuous smartphone use. Continuous use was determined by the sum of these episodes divided by the number of days the app was running. Smartphone use and continuous use were calculated for schooldays and non-schooldays separately. Non-schooldays consisted for 75.5% of weekend days and 24.5% of holidays. The density plots of smartphone use and continuous smartphone use during schooldays defined by the three different data processing manners are shown in Figure S2.

Validation study

We performed a validation study which included 5 Android users and 5 iOS users; they installed the Myopia app on their smartphone for two weeks. Smartphone use measured by the Myopia app was compared with smartphone use measured by the inbuilt screen time tracker of the smartphone. The Spearman correlation coefficient between the smartphone use measured by the Myopia app and the smartphone use measured by the inbuilt app was calculated.

Face to screen distance

Face to screen distance was measured using the front camera of the smartphone. Android device users calibrated the app by holding their smartphone exactly 29.7 cm in front of their eyes (the length of the long side of an A4 paper); IOS device users did not need to calibrate face to screen measurement because of the technical similarities among iPhones. Face to screen distance was measured when the app was active and open (i.e. when participants were filling out questions). The number of face to screen measurements was on average 592 (SD 1246;

median 272.0; IQR 403.3) times per person. Mean face to screen distance was calculated. Sensitivity analyses were performed excluding participants with <100 measurements to ensure that measurement reflected most common used smartphone distance.

Outdoor exposure

Outdoor exposure was asked repeatedly in the app for five weeks. On Monday afternoon, and Friday evening, the participants received the question: How much time did you spend outdoors last Saturday/Sunday/Monday or Tuesday/Wednesday/Thursday/Friday? For example cycling, sports, walking, playing outdoors, or being outdoors with friends or family. Mean outdoor exposure per day (in hours per day) was calculated for schooldays and non-school days separately.

Other covariates

Sex, age at examination, season of app measurement, ethnic background and operating system (iOS or Android) were considered as covariates. Ethnic background was defined according to the definitions by Health Statistics Netherlands, i.e. based on the country of birth of the (grand) parents; it was assessed through a questionnaire in the app for the MAS participants, and by questionnaires filled out by the parents for the Generation R participants, and stratified into European and non-European. Operating system was assessed through the app.

Eye measurements

The eye exam consisted of presenting monocular visual acuity with LogMAR based ETDRS-charts at 3 meter distance by means of the fast ETDRS method. Ocular biometry was measured by Zeiss IOL-master 500 or 700 (Carl Zeiss MEDITEC IOL-master, Jena, Germany). Five axial length measurements per eye were averaged to mean axial length; three measurements of corneal radius (K1 and K2) were averaged to mean corneal radius (CR), and axial length corneal radius (AL/CR) ratio was calculated. Cycloplegic refractive error of the non-dominant eye was measured with handheld Retinomax 3 (Righton, Japan) in the MAS participants, of both eyes in the Generation R participants, both 30 minutes after 2 dosages of cyclopentolate 1%. Spherical equivalent of refraction (SER) was calculated by the sum of the full spherical value plus half of the negative cylindrical value. Mean SER for Generation R participants was assessed by averaging SER of the right and left eye. Myopia was defined as SER≤-0.50 dioptre (D).

Data analyses

Differences between participants who were included in the analyses and who were excluded due to missing data, as well as differences between the school based cohort and Generation R were analysed with independent t-tests for continuous variables and chi-square tests for dichotomous variables. Spearman correlation coefficients were calculated between smartphone use, continuous use, face to screen distance and outdoor exposure during schooldays and weekend days. In order to take into account the similarities between teenagers from the same study site, linear mixed models with restricted likelihood estimation from the nlmer package in R were used to perform the analyses.[22] The association between smartphone use, continuous use (20 min), outdoor exposure and face to screen distance as exposures and SER and AL/CR as outcomes variables were investigated, with random intercept for study sites (schools), and adjusted for age, sex, season of app measurement and operating system (iOS or Android). The following sensitivity analyses were performed: First, outliers in smartphone use and continuous use were excluded, i.e. >4 / 6 hours continuous use, and days with <1 / 10 minutes smartphone use (see above). Second, we additionally adjusted for outdoor exposure to ensure an independent association between smartphone use, continuous use and SER and AL/CR. Third, participants with less than 100 measurements for face to screen distance were excluded (see above). Fourth, due to the large number of missing data for ethnicity and because the MAS participants were 97% European, we did not adjust for ethnicity in the main analyses but performed sensitivity analyses with European participants only. Finally, interaction analysis was performed with smartphone use, outdoor exposure and an interaction-term as exposures and SER and AL/CR as outcomes variables, with random intercept for study sites (schools), and adjusted for age, sex and operating system. Stratified analyses were performed for teenagers with high and low outdoor exposure based on the median. Analyses were performed in IBM SPSS version 25 and R statistical software version 3.6.1.[23,24]

RESULTS

The teenagers were on average 13.7 (0.85) years old; 54% were girls. Myopia prevalence was 18.9%, SER was +0.40 (1.90) D, AL/CR was 2.99 (0.11), and axial length 23.4 (0.88) mm. The teenagers spent on average 3.71 (1.70) hr/day on their smartphone on schooldays and 3.82 (2.09) hr/day on non-school days with an average face to screen distance of 29.1 (6.25) cm. Participants had 6.42 (4.36) episodes of 20 minutes continuous use per day during schooldays and 7.10 (5.28) during non-school days. Outdoor exposure was 2.37 (0.94) hr/day on schooldays and 2.77 (1.13) hr/day on non-school days. Participants with myopia had a more negative SER, larger AL/CR and axial length, compared to participants without myopia. Differences between participants with (n=45) and without (n=193) myopia regarding sex,

ethnicity, smartphone use, continuous use, face to screen distance, outdoor exposure, season of app measurement, operating system and study site did not reach statistical significance (Table 1).

Table 1. General characteristics

	Total (n=272)	Missing (%)	Myopia (n=45)	No myopia (n=193)	P-value
Age (±SD; years)	13.7 (0.85)	0.0	13.5 (0.96)	13.7 (0.87)	0.36
Sex (% ♀)	53.7	0.0	60.0	52.3	0.41
Ethnicity (% European)	86.5	15.4	81.8	87.7	0.39
Spherical equivalent (±SD; dioptres)	0.40 (1.90)	12.5	-2.36 (2.10)	1.04 (1.11)	<0.001
Myopia (%)	18.9	12.5	NA	NA	NA
Axial length corneal radius ratio (±SD)	2.99 (0.11)	2.6	3.14 (0.13)	2.96 (0.08)	<0.001
Axial length (±SD; mm)	23.4 (0.88)	0.4	24.2 (0.91)	23.2 (0.73)	<0.001
Smartphone use (±SD; hr/day)					
During schooldays	3.71 (1.70)	7.7	3.75 (1.55)	3.67 (1.73)	0.78
During non-school days	3.82 (2.09)	5.9	3.54 (2.11)	3.77 (2.09)	0.52
Continuous use (episodes of ≥20 min; ±SD)					
During schooldays	6.42 (4.36)	7.7	6.62 (4.32)	6.13 (4.17)	0.50
During non-school days	7.10 (5.28)	5.9	6.51 (5.95)	6.91 (5.11)	0.66
Face to screen distance (±SD; cm)	29.1 (6.3)	14.7	29.1 (7.47)	29.4 (5.72)	0.76
Outdoor exposure (±SD; hr/day)					
During schooldays	2.37 (0.94)	11.8	2.10 (0.90)	2.41 (0.96)	0.06
During non-school days	2.77 (1.13)	1.5	2.48 (1.21)	2.83 (1.07)	0.05
Season app measurement (%);		0.0			0.65
Spring	71.3		66.6	72.0	
Summer	20.2		20.0	19.2	
Autumn	8.5		13.3	8.8	
Operating System (% Android)	60.7	0.0	68.9	59.1	0.24
Study site		0.0			0.16
Generation R	25.7		22.2	15.5	
School 1	36.4		28.9	44.6	
School 2	13.6		20.0	14.0	
School 3	8.8		11.1	8.3	
School 4	4.0		0.0	5.7	
School 5	4.0		8.8	3.6	
School 6	7.4		8.8	8.3	

SD: standard deviation; Hr/day: hours per day; Min: minutes; Cm: centimetres

Variables that differed between the MAS cohort and Generation R were age (p=0.02), ethnic background (p<0.001), and outdoor exposure during schooldays (p=0.01). Participants who were included in the analyses were younger (13.7 versus 13.9 years; p=0.01) and more often

from European ethnic background (86.5% versus 67.9%; p≤0.001) than those who were not included due to missing data on smartphone use and eye measurements. Differences between children included in the analysis and those excluded regarding sex, SER, myopia, axial length and AL/CR were not observed. The Spearman correlation coefficient between the Myopia app and the inbuilt app in our validation study was 0.97 (Figure S3).

Correlations between smartphone use, face to screen distance and outdoor exposure are depicted in Figure 1. Smartphone use, face to screen distance and outdoor exposure were normally distributed, continuous use was slightly right skewed (Figure S2). Smartphone use was strongly correlated with continuous use (r=0.86, p<0.001 during schooldays; r=0.90, p<0.001 during weekend days) and outdoor exposure was inversely correlated with smartphone use and continuous use (smartphone use: r=-0.19, p=0.006 during schooldays; r=-0.21, p=0.003 during weekend days; continuous use: r=-0.24, p<0.001 during schooldays; r=-0.26, p<0.001 during weekend days). Face to screen distance was not correlated with smartphone use, continuous use, or outdoor exposure.

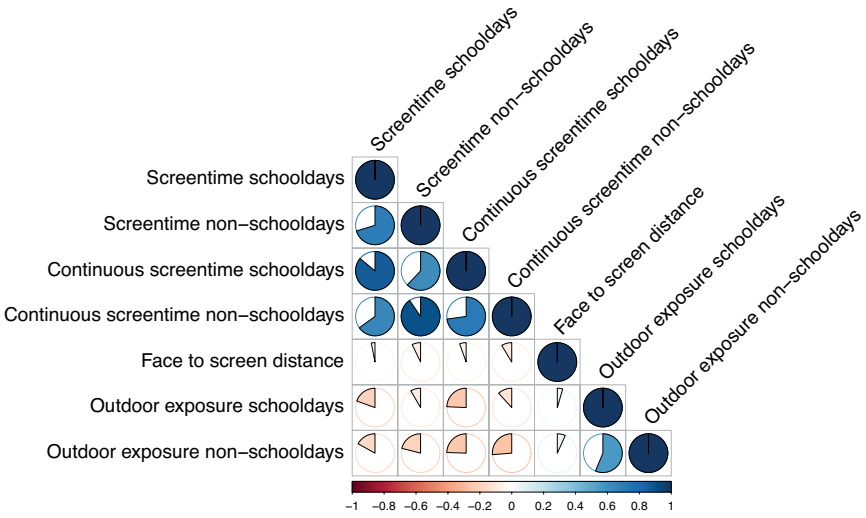

Figure 1. Correlations between smartphone use, continuous use, face to screen distance and outdoor exposure during schooldays and holidays. Dark blue represents a positive correlation of 1 while dark red represents a negative correlation of -1.

Continuous use during schooldays was associated with SER (per each extra episode of 20 minutes continuous use: β=-0.07, 95%CI=-0.13, -0.01) and AL/CR (β=0.004, 95%CI=0.001, 0.008; Figure 2). Smartphone use during schooldays showed a similar trend and was

borderline significantly associated with AL/CR (β=0.008, 95%CI=-0.001, 0.017), but not with SER (β=-0.09, 95%CI=-0.25, 0.07). Outdoor exposure was associated with SER (β=0.33, 95%CI=0.07, 0.60; β=0.32, 95%CI=0.10, 0.55 both during schooldays), and with AL/CR during non-schooldays (β=-0.016, 95%CI=-0.029, -0.003). Face to screen distance, continuous use during non-school days, and smartphone use during non-school days were not associated with SER or AL/CR (Table 2). Sensitivity analyses with different definitions of smartphone use, or adjustment for outdoor exposure yielded similar results; excluding non-Europeans and those with missing data on ethnicity resulted in similar, albeit not significant, beta-coefficients. Face to screen distance excluding participants with <100 measurements was not significantly associated with SER or AL/CR (Table S2).

Stratified analyses showed that the association between continuous use and SER and AL/CR was observed for teenagers with low outdoor exposure (β=-0.10, 95%CI=-0.20, -0.01 for SER and β=0.007, 95%CI=0.001, 0.013 for AL/CR), but not for teenagers with high outdoor exposure (Table 3). However, the interaction term between continuous use and outdoor exposure was not significant (p=1.00 for SER; p=0.40 for AL/CR).

Table 2. Linear regression analyses of smartphone use, continuous use during schooldays and non-schooldays, and face to screen distance on spherical equivalent and axial length corneal radius ratio.

	N	Estimate	SE	95% CI		P-value
SER						
Smartphone use (hr/day) during schooldays	207	-0.09	0.08	-0.25	0.07	0.30
Continuous use (≥20 min) during schooldays	207	-0.07	0.03	-0.13	-0.01	0.03
Smartphone use (hr/day) during non-school days	204	-0.02	0.10	-0.21	0.18	0.88
Continuous use (≥20 min) during non-school days	204	-0.03	0.03	-0.11	0.04	0.34
Outdoor exposure (hr/day) during schooldays	213	0.33	0.13	0.07	0.60	0.01
Outdoor exposure (hr/day) during non-schooldays	235	0.32	0.11	0.10	0.55	0.004
Face to screen distance	201	0.00	0.02	-0.04	0.04	0.98
AL/CR						
Smartphone use (hr/day) during schooldays	227	0.008	0.005	-0.001	0.017	0.10
Continuous use (≥20 min) during schooldays	227	0.004	0.002	0.001	0.008	0.02
Smartphone use (hr/day) during non-school days	226	0.002	0.006	-0.010	0.013	0.75
Continuous use (≥20 min) during non-school days	226	0.002	0.002	-0.002	0.006	0.29
Outdoor exposure (hr/day) during schooldays	235	-0.011	0.008	-0.027	0.005	0.17
Outdoor exposure (hr/day) during non-schooldays	261	-0.016	0.006	-0.029	-0.003	0.02
Face to screen distance	226	0.000	0.001	-0.003	0.002	0.84

Adjusted for age, sex, season of app measurement and operating system; Hr/day: hours per day; Min: minutes

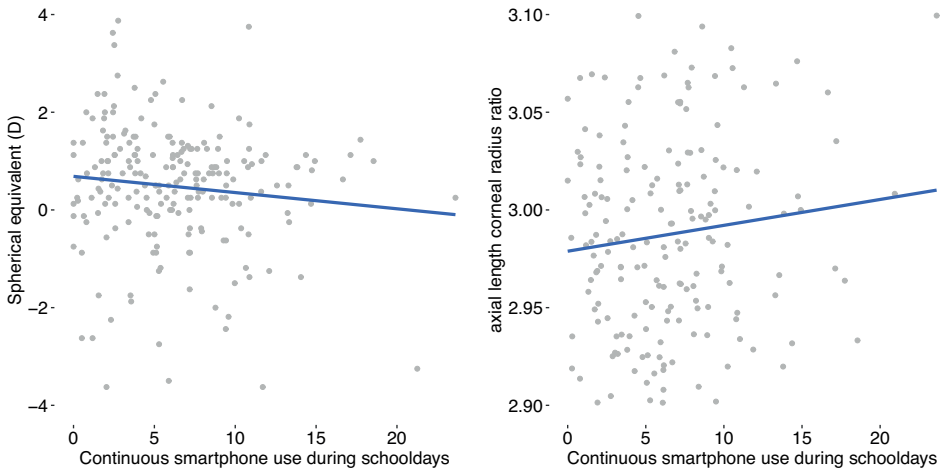

Figure 2. Association between continuous smartphone use (episodes of ≥20 min) and spherical equivalent (left), and axial length corneal radius ratio (right). Blue lines represent the unadjusted regression lines.
D: dioptre; Min: minutes

Table 3. Linear regression analyses of smartphone use and continuous use during schooldays and holidays on spherical equivalent and axial length corneal radius ratio stratified by high versus low outdoor exposure.

		N	Estimate	SE	95% CI		P-value
SER							
low outdoor exposure	Smartphone use (hr/day) during schooldays	99	-0.12	0.13	-0.36	0.12	0.35
	Continuous use (≥20 min) during schooldays	99	-0.10	0.05	-0.20	-0.01	0.03
high outdoor exposure	Smartphone use (hr/day) during schooldays	99	-0.04	0.11	-0.25	0.17	0.72
	Continuous use (≥20 min) during schooldays	99	-0.02	0.05	-0.12	0.07	0.61
AL/CR							
low outdoor exposure	Smartphone use (hr/day) during schooldays	112	0.010	0.007	-0.004	0.024	0.17
	Continuous use (≥20 min) during schooldays	112	0.007	0.003	0.001	0.013	0.02
high outdoor exposure	Smartphone use (hr/day) during schooldays	105	0.003	0.006	-0.009	0.014	0.65
	Continuous use (≥20 min) during schooldays	105	0.001	0.002	-0.003	0.006	0.59

Adjusted for age, sex, season of app measurement and operating system; Hr/day: hours per day; Min: minutes

DISCUSSION

In this study, we used a mobile application to determine smartphone use in relation to refractive error. We showed that those with more episodes of continuous use had a more myopic refractive error. This association disappeared in teenagers with high outdoor exposure, suggesting that outdoor exposure may moderate this effect.

Smartphone use is a relatively new behavior among our youth. It became increasingly popular after the introduction of the first iPhone in 2008. Worldwide, 139 million smartphones were sold in 2008 which increased to 1496 million smartphone in 2016. Most smartphone owners are from the United States and Western Europe, but the Chinese market is also on the rise.[25] Research reports addressing the effect of smartphone use on myopia in teenagers are scarce. In our study, smartphone use was 3.71 hr/day during schooldays according to our Myopia app, which is comparable with the 4 hr/day among 19-year-old university students from the United States measured with the app *Moment*.[17] A Chinese study showed that one hour/day increase in smartphone use was associated with -0.28 D SER, after adjustment for age, sex, reading behavior, outdoor exposure and sleep in 566 6-14 year old children.[26] We observed a particular association with continuous use; SER was -0.07 D more myopic and AL/CR 0.005 larger for each extra episode of 20 minutes continuous use. SER was -0.10 D more myopic and AL/CR 0.008 larger for each hour of daily smartphone use, but this association was not significant (p=0.22 for SER and p=0.07 for AL/CR). Studies focusing on reading behavior also reported that continuous reading was more prominently associated with myopia than total reading time,[12,27] despite their high correlation. Continuous near work may be a more important risk factor than time spent on near work, suggesting that regular breaks during near work (including smartphone use) will help prevent teenagers from myopia.

While the association between screen time and myopia was debatable for a long time,[28,29] recently the results of many studies support the presence of such an association.[30-34] Exposure to screen time before the age of 1 was associated with myopia (prevalence ratio 4.02) among 26,433 pre-school children in China.[30] Irish school children who spent >3 hr/day on a screen were more often myopic (odds ratio 3.70), and 1 hour increase in computer use was associated with myopia (odds ratio 1.005) in our former study among 9 year old children.[31,32] Adolescents using a screen for >6 hr/day were more often myopic than those with <2 hr/day screen use (odds ratio 1.95) in Copenhagen.[33] A longitudinal study among 5-15 year old children from India showed that >7 hr/day screen time was also associated with myopia progression compared to <4 hr/day screen time (odds ratio 3.53).[34] Together with our current findings, this suggests that screen use may become an established risk factor for myopia.

Reading distance has been identified as a risk factor for myopia in many cross-sectional and longitudinal studies.[12,27,32,35] Reading distance was often measured using a questionnaire for parents, and these studies reported positive associations for 30 cm,[27,32] 20 cm[12] and 33 cm.[35] The sensitivity analysis in our study showed that 1 cm shorter face to screen distance was associated with -0.03 D (95% CI: 0.02, -0.08) more myopia, but this association failed to reach statistical significance. Face to screen distance was not correlated with smartphone use in our study. Ip et al (2008) and Li et al (2015) did not identify a correlation between reading distance and reading time either, adding to the discrepancies in the associations with refractive error for continuous smartphone use and face to screen distance.[12,27]

Strengths of this study are the objective measurement of smartphone use and face to screen distance using the Myopia app. The Myopia app was made available for both iOS and Android devices, thus accessible to almost any smartphone user. Our validation study showed a high correlation between smartphone use measured by the Myopia app and smartphone use measured by the inbuilt screen time tracker of the smartphone, supporting an accurate registration. Sensitivity analyses with different definitions of smartphone use yielded similar results, indicating that the association was robust. Nevertheless, some limitations should be borne in mind. First, the cross-sectional design of this study hindered causal interpretation of the data. Current smartphone use most likely reflects previous smartphone use, however, cumulative smartphone use depends on the age of smartphone acquisition. In the Netherlands, most children own a smartphone from the age of 10 years onwards,[36] and we expect that most teenagers in our study already had 2-3 years of smartphone exposure time. Second, the relatively large number of days with unrealistic measurements and the limited sample size may have led to inconclusive results. Future studies should incorporate a longitudinal study design in a large sample. Third, some activities on the smartphone, like calling someone, were registered as smartphone use, while not involving near work. Yet, since time spent on calling is usually very short in teenagers of this age, we do not expect that this had a major influence on our results.[36] Finally, only the non-dominant eye was measured with cycloplegia in the MAS participants. Non-dominant eyes may be more hyperopic than dominant eyes in children with anisometropia.[37,38] This may have resulted in an underrepresentation of myopia in the MAS participants, but did not distort AL/CR as this was measured in both eyes.

In conclusion, our study showed that Dutch teenagers use their smartphone almost 4 hours per day. A higher number of episodes of >20 minutes continuous use was associated with more myopic SER and a larger AL/CR. This association was not present in teenagers with high outdoor exposure, suggesting that outdoor exposure moderates the association. Since smartphone use is becoming increasingly popular, awareness of the potential negative consequences of prolonged smartphone use is warranted. The 20-20-2 rule as recommended earlier remains good advice.[39]

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SUPPLEMENTS

Table S1. Linear regression analyses of smartphone use and continuous use during schooldays and holidays on spherical equivalent and axial length corneal radius ratio.

		SER					
		N	**Estimate**	**SE**	**95% CI**		**P-value**
Excl. days with >4 hours continuous and <1 min smartphone use	Smartphone use (hr/day) during schooldays	207	-0.06	0.08	-0.22	0.10	0.47
	Continuous use (≥20 min) during schooldays	207	-0.06	0.03	-0.13	0.01	0.07
	Smartphone use (hr/day) during holidays	204	0.01	0.10	-0.19	0.21	0.91
	Continuous use (≥20 min) during non-school days	204	-0.03	0.04	-0.10	0.05	0.47
Excl. days with >6 hours continuous and <10 min smartphone use	Smartphone use (hr/day) during schooldays	207	-0.09	0.08	-0.25	0.07	0.29
	Continuous use (≥20 min) during schooldays	207	-0.06	0.03	-0.13	-0.003	0.04
	Smartphone use (hr/day) during non-school days	204	-0.05	0.10	-0.25	0.15	0.62
	Continuous use (≥20 min) during non-school days	204	-0.05	0.04	-0.12	0.02	0.17
Additionally adjusted for outdoor exposure	Smartphone use (hr/day) during schooldays	200	-0.08	0.08	-0.24	0.08	0.32
	Continuous use (≥20 min) during schooldays	200	-0.07	0.03	-0.13	-0.004	0.05
	Smartphone use (hr/day) during non-school days	203	0.05	0.06	-0.08	0.18	0.42
	Continuous use (≥20 min) during non-school days	203	0.01	0.03	-0.04	0.06	0.71
European participants only	Smartphone use (hr/day) during schooldays	151	-0.05	0.10	-0.25	0.15	0.62
	Continuous use (≥20 min) during schooldays	151	-0.05	0.04	-0.13	0.04	0.64
	Smartphone use (hr/day) during non-school days	150	0.01	0.11	-0.20	0.22	0.91
	Continuous use (≥20 min) during non-school days	150	-0.01	0.04	-0.08	0.07	0.87
Excl. participants with <100 measurements	Face to screen distance	178	0.03	0.02	-0.02	0.08	0.20

Adjusted for age, sex, season of app measurement and operating system; Hr/day: hours per day; Min: minutes; Excl.: excluding

AL/CR					
N	Estimate	SE	95% CI		P-value
227	0.006	0.005	-0.003	0.015	0.21
227	0.004	0.002	0.000	0.008	0.05
226	0.000	0.006	-0.012	0.012	1.00
226	0.002	0.002	-0.003	0.006	0.46
227	0.006	0.005	-0.003	0.016	0.19
227	0.003	0.002	0.000	0.007	0.07
226	0.003	0.006	-0.008	0.015	0.57
226	0.003	0.002	-0.001	0.007	0.17
219	0.006	0.005	-0.003	0.015	0.18
219	0.004	0.002	0.0004	0.008	0.03
226	-0.002	0.004	-0.009	0.006	0.63
226	0.0001	0.001	-0.003	0.003	0.95
170	0.003	0.005	-0.007	0.014	0.56
170	0.002	0.002	-0.002	0.007	0.28
173	0.001	0.006	-0.010	0.012	0.88
173	0.000	0.002	-0.003	0.005	0.77
195	-0.001	0.002	-0.004	0.002	0.53

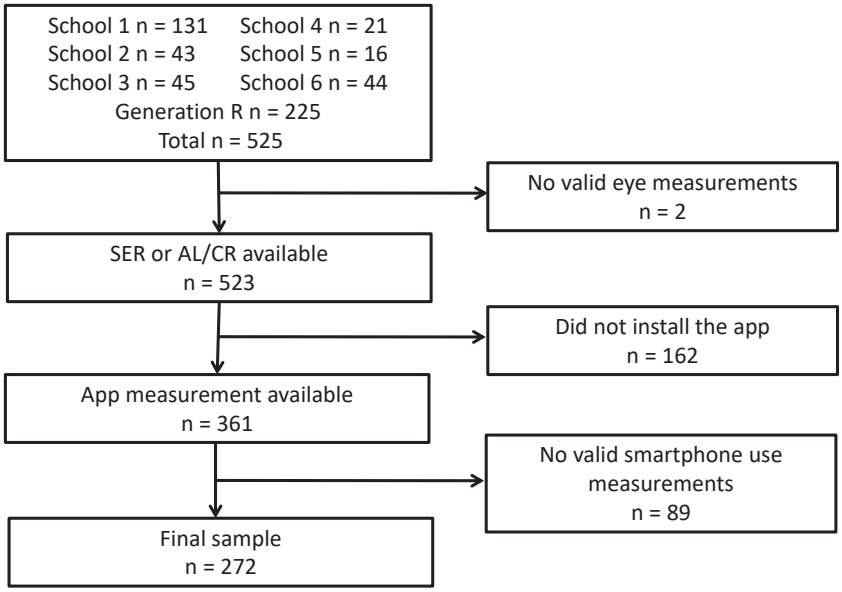

Figure S1. Flowchart of the study

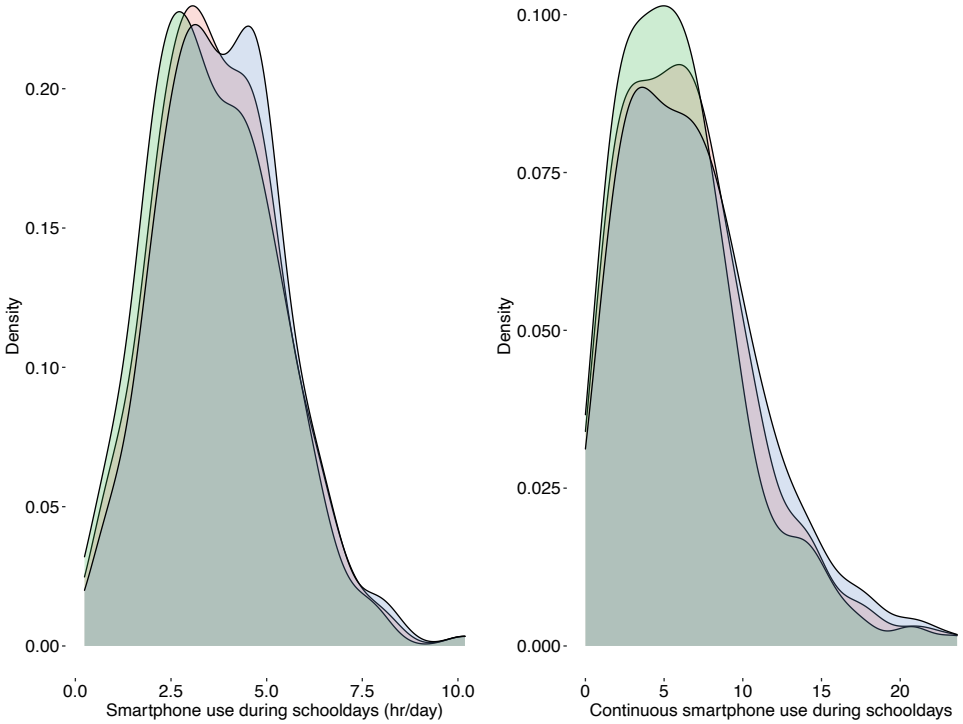

Figure S2. Smartphone use during schooldays (hr/day, left) and continuous use during schooldays (≥20 min, right), excluding days with less than 1 (green), less than 5 (red) and less than 10 (blue) minutes of smartphone use in total, or days with more than 4 (green), 5 (red) and 6 (blue) hours continuous use.
Hr/day: hours per day; Min: minutes

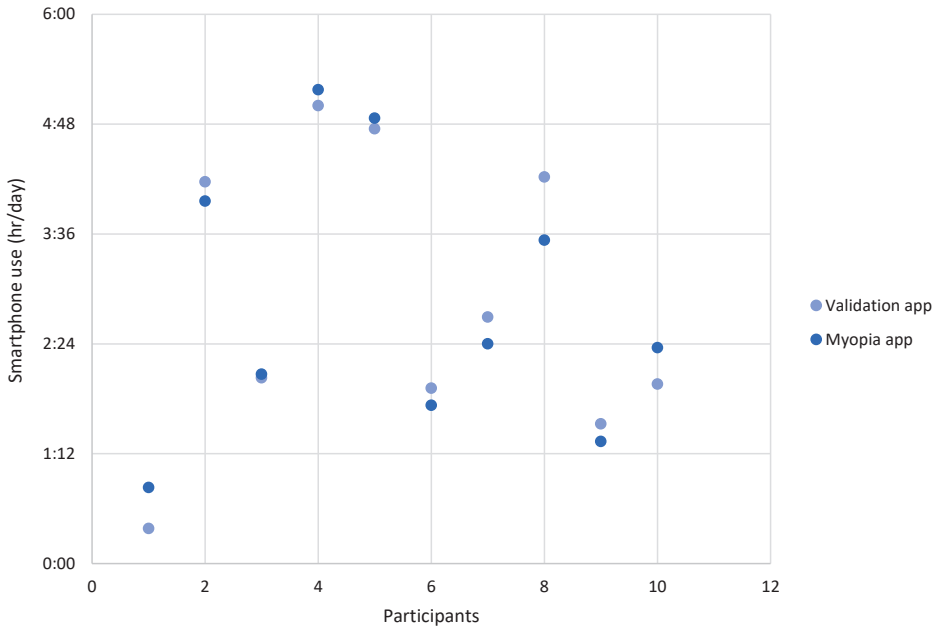

Figure S3. Smartphone use per day on the y-axis measured by the Myopia app (dark blue) and another validation app (light blue) for 10 participants depicted on the x-axis. The Spearman correlation coefficient between the measurements of both apps is 0.97.
Hr/day: hours per day; Min: minutes

8

Physical activity spaces not effective against socioeconomic inequalities in myopia incidence. The Generation R study

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ABSTRACT

Significance: Our findings show that non-Dutch background, lower maternal education and lower net household income level may be new risk factors for myopia development in the Netherlands. Newly introduced physical activity spaces may not be effective enough in increasing outdoor exposure in children in order to reduce eye growth.

Purpose: The aims of this study were to evaluate socioeconomic inequalities in myopia incidence, eye growth, outdoor exposure and computer use, and to investigate if newly introduced physical activity spaces can reduce eye growth in school-aged children.

Methods: Participants (n=2643) from the Dutch population-based birth cohort Generation R were examined at ages 6 and 9 years. Socioeconomic inequalities in myopia incidence, eye growth and lifestyle were determined using regression analyses. Information on physical activity spaces located in Rotterdam was obtained. Differences in eye growth between those who became exposed to new physical activity spaces (n=230) and those non-exposed (n=1866) were evaluated with individual level fixed-effects models.

Results: Myopia prevalence was 2.2% at 6 years and 12.2% at 9 years. Outdoor exposure was 11.4 hours/week at 6 years and 7.4 hours/week at 9 years. Computer use was 2.1 hours/week at 6 years, and 5.2 hours/week at 9 years. Myopia incidence was higher in children with non-Dutch background, families with lower household income and lower maternal education (OR=1.081, 95%CI=1.052-1.112; OR=1.035, 95%CI=1.008-1.063; OR=1.028, 95%CI=1.001-1.055; respectively). Children living <600 meters of a physical activity space did not have increased outdoor exposure, except those from families with lower maternal education (β=1.33 hours/week, 95%CI=0.15-2.51). Newly introduced physical activity spaces were not associated with reduction of eye growth.

Conclusion: Children from socioeconomically disadvantaged families became more often myopic than those from socioeconomically advantaged families. We did not find evidence that physical activity spaces protect against myopia for the population at large, but subgroups may benefit.

INTRODUCTION

Myopia (near-sightedness) is a common refractive error in urban areas. The prevalence in Europe has risen dramatically from 25% of the young adults 30 years ago to 50% of the young adults today.[1] In China, up to 80% of the university students in China is myopic.[2] Higher degrees of myopia are associated with increased prevalence of complications, such as myopic macular degeneration, retinal detachment, and/or glaucoma. These complications may cause irreversible visual impairment or blindness, particularly in persons with high myopia.[3]

The dramatic increase in myopia prevalence is likely triggered by the changing lifestyle in childhood with increasing near work and lack of outdoor exposure.[4-6] Outdoor exposure has received considerable attention in myopia research.[6] Randomized controlled trials have been conducted in several Asian countries to evaluate whether myopia can be prevented by increasing outdoor time at school. The results consistently showed that children in the intervention group had less myopia compared to their peers.[6, 7] Some non-school program interventions suggested that a supportive neighbourhood can promote outdoor play by providing opportunities to play outdoors.[8-10] We recently observed socioeconomic inequalities in 6 years olds from the Generation R Study: children from families with low income and low education had an increased prevalence of myopia, mostly due to a higher frequency of lifestyle factors .[11] Children from disadvantaged families often receive fewer opportunities to be outside and seem to perform more continuous near work.[11-14] Creating an environment that is supportive for outdoor play behaviour may be an effective policy for myopia prevention.

Two foundations established by Dutch sports legends (Richard Krajicek, former professional tennis player, Wimbledon champion; Johan Cruyff, former professional soccer player and coach) introduced new physical activity spaces in Dutch cities to encourage outdoor play, with a special focus on children living in deprived neighbourhoods. The new physical activity spaces target children aged 6–18 years and contain one or more of the following: soccer field, basketball court, tennis field or playground equipment. Some physical activity spaces additionally contain a mini-athletics track, panna-court, tennis table, skating rink, fitness items, volleyball field, or dance floor. The first Krajicek Playground in Rotterdam, the Netherlands was opened in 2001; the first Cruyff Court was opened in 2005.[15, 16]

Earlier research suggested that the introduction of these physical activity spaces in Rotterdam may increase outdoor play for children from socioeconomically disadvantaged families.[15] The extent to which changes in the physical environment of the neighbourhood can promote outdoor play, and subsequently reduce the risk of incident myopia or eye growth, is currently unknown. The purpose of this study is (1) to evaluate potential socioeconomic inequalities in

myopia incidence, eye growth, outdoor exposure and computer use in school aged children and (2) whether newly introduced physical activity spaces can reduce eye growth, especially in children from socioeconomically disadvantaged families.

METHODS

Study population: Generation R

Generation R is a population-based prospective cohort of 9778 pregnant women and their children who were born between April 2002 and January 2006 in Rotterdam, The Netherlands. The exact methodology of the Generation R study has been described elsewhere.[17] We used data from children who were invited to the research centre when they were 6 and 9 years old. Of the initial cohort, 5431 (55.5%) children participated at both visits. Children who no longer lived in Rotterdam, and children with a missing or invalid residential address at age 6 or 9 years were excluded (n=2447). Children with missing data on axial length at age 6 or 9 years were also excluded (n=341). The final sample consisted of 2643 children, 547 already had access (<600 m) to a physical activity space at 6 years, 230 gained access (<600 m) to a new physical activity space at 9 years, and 1866 did not have access (>600 m) to a physical activity space during this study period. The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam (MEC 217.595/2002/20), and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Eye measurements

Ocular biometry was measured by Zeiss IOL-master 500 at age 6 and 9 years (Carl Zeiss MEDITEC IOL-master, Jena, Germany). For axial length five measurements per eye were averaged to mean axial length (mm). Three measurements of corneal curvature were taken of both eyes, and mean corneal radius was calculated. Mean axial length/corneal radius ratio was calculated by dividing axial length (mm) by corneal radius (mm) for both eyes, and then averaged. Eye growth was defined as mean axial length/corneal radius ratio change (per year) and axial elongation (mm/year); by subtracting axial length/corneal radius ratio or axial length at age 6 from axial length/corneal radius ratio or axial length at age 9 per eye, divided by the time between the measurements in years and was then averaged. Visual acuity was measured with LEA charts at a 3-m distance by means of the Early Treatment Diabetic Retinopathy Study method at age 6 and 9 years.[18] In children with visual acuity of worse than 0.1 logarithm of the minimum angle of resolution (LogMAR; Snellen visual acuity <0.8) in at least 1 eye, or in children with an ophthalmologic history automated cycloplegic refractive error was performed using a Topcon KR8900 instrument (Topcon, Japan). Those with visual acuity of 0.1 LogMAR or better who had no glasses and no ophthalmic history were classified as non-myopic.[19]

Two drops (three in case of dark irises) of cyclopentolate (1%) with 5 minutes interval were dispensed, and refractive error measurements were performed at least 30 minutes thereafter when pupil diameter was ≥6 mm. Automated cycloplegic refractive error measurement regardless of visual acuity was introduced for all children during the research phase at 9 years. Spherical equivalent was calculated as the sum of the full spherical value and half of the cylindrical value. Myopia was defined as spherical equivalent ≤-0.50 dioptre in at least one eye.

Outdoor exposure and computer use

Outdoor play was measured using a questionnaire filled in by the parents. At 6 years, the questions "how many days per week does your child play outside" and "approximately how long does your child play outside per day" were asked for weekend and weekdays separately. Mean weekly outdoor play was calculated by multiplying the number of days by time in minutes. Walking or cycling to and from school and computer use was processed similarly. Total outdoor exposure was calculated as the sum of playing outside and walking or cycling to and from school. At 9 years, similar questions were asked regarding outdoor play, walking or cycling to and from school and computer use, although the question options did not specify weekend and weekdays separately.

Socioeconomic determinants

Maternal education level when the child was 6 years old was categorized into higher (bachelor's degree, higher vocational training, university degree), and lower (less than bachelor's degree) education level based on self-report. Net household income (low: ≤€3200/month, high: >€3200/month) was collected at both time points. If net household income was missing at age 6, the income measured at age 9 was imputed 9 (n=126) and vice versa (n=120). In accordance with Statistics Netherlands, a child's family background was classified as Dutch with or without migration based on the country of birth of the child's parents, further referred to as Dutch and non-Dutch background.

The intervention: Exposure to dedicated physical activity spaces

The foundations provided information about the location of the physical activity spaces and the date of opening. They considered neighbourhoods eligible for a physical activity space when they were deprived of accessibility to sports/play facilities, had low physical activity levels or sport participation rates among youth, or could otherwise show that the introduction of physical activity spaces was likely to benefit children's development. The physical activity spaces were freely accessible and often supervised during peak hours. More information on the physical activity spaces can be found on the websites of the foundations: www.krajicek.nl and www.cruyff-foundation.org. The distance of the nearest physical activity space for each Generation R child was determined using the software QGIS.[20] A buffer size of 600 meters was

chosen based on the mean radius of a Rotterdam neighbourhood in 2008.[21] Euclidian buffers of 600 meters around children's homes were calculated, and the presence of existing and new dedicated physical activity spaces within buffers was determined at the age of 6 and 9 years.

Statistical analyses

Baseline characteristics were presented using mean and standard deviation for continuous variables, and percentages for categorical variables. The proportion of higher versus lower maternal education and household income was assessed for children with Dutch and non-Dutch background using chi-square tests. Myopia incidence (n=240/2467) was considered a dichotomous outcome variable; axial length/corneal radius ratio change (n=2643) and axial elongation (n=2643) were processed as continuous outcomes.

Socioeconomic inequalities in myopia incidence, eye growth, outdoor exposure and computer use

First, we assessed socioeconomic inequalities and ethnic differences in outdoor exposure and computer use at age 6 and 9 years using linear regression analyses adjusted for age, sex and season of data collection. Second, we tested socioeconomic inequalities and ethnic differences in myopia incidence, axial length/corneal radius ratio change, and axial elongation by logistic and linear regression analyses adjusting for age and sex. Finally, we additionally adjusted for outdoor exposure, computer use and season of data collection at age 6 years to determine whether the identified associations could, in part, be explained by these factors.

Exposure to physical activity spaces and outdoor exposure

We included only those children without access to a physical activity space within their neighbourhood (<600m from their home) at age 6 years (n=2096). First, we assessed the association between exposure to newly introduced physical activity spaces between 6 and 9 years as determinant and outdoor exposure at 9 years and change in outdoor exposure from 6 to 9 years as outcomes using linear regression analyses adjusted for age, sex, and season of data collection. Second, we conducted the analyses separately for children with a Dutch and non-Dutch background, from families with lower and higher net household income at baseline and lower and higher educated mothers.

Exposure to physical activity spaces and eye growth

Fixed-effect models were used to estimate the within-person changes in exposure to physical activity spaces and within-person changes in the continuous outcomes axial length/corneal radius ratio and axial length. They allowed to control for unmeasured time-invariant and measured time-variant confounders, we therefore adjusted for the time-varying covariates age, and season of data collection, and additionally for net household income and computer use.[22] Fixed-effect models for binary outcome variables will drop observations for whom myopia

status did not change over time, yielding considerable power issues and myopia incidence was therefore not investigated. Again, these analyses were conducted separately for children from families with lower and higher net household income at baseline, lower and higher educated mothers, and with a Dutch and non-Dutch background. The following sensitivity analyses were performed: First, we excluded children who were already myopic at 6 years from the analyses, because their eyes may grow faster than those who were not yet myopic. Second, we repeated the analyses using buffers of 400 and 800 m to explore whether effects reported were sensitive to the size of buffers. Third, we excluded children for whom the data were collected within 6 months after the introduction of the new physical activity space, to account for the novelty effect and assure that long-term impact is obtained. Fourth, we excluded children who moved houses within the study period. All analyses were conducted in R statistical software version 3.6.1, using the *plm* package for the fixed-effects analyses.[23, 24]

RESULTS

The study cohort consisted of 2643 children with mean age 6.1 at baseline, 9.8 at follow-up; 50.5% were female, and 63% had a Dutch background. Parents from children with non-Dutch background were mostly from Africa (8.8%), Europe (8.5%), Suriname (6.5%), Turkey (5.8%) and Asia (3.3%). Almost half of the children had a mother with low education level (41.1%), and a low net household income (48.4%). Myopia prevalence was 2.2% at age 6 years, which increased to 12.2% at age 9 years. Outdoor exposure was 11.4 hours/week at age 6, which decreased to 7.4 hours/week at age 9, while computer use was 2.1 hours/week and 5.2 hours/week, respectively (Table 1). Families with a Dutch background more often had a higher educated mother (67.8% versus 43.8%, p<0.001) and higher household income (65.2% versus 28.7%, p<.001) than families with a non-Dutch background.

Children with non-Dutch background had -1.46 (95%CI=-2.10; -0.82) and -0.55 (95%CI=-0.96; -0.14) hours/week outdoor exposure at 6 and 9 years, and 0.97 (95%CI=0.72-1.22) and 1.33 (95%CI=0.87-1.80) hours/week more computer use at 6 and 9 years than those with Dutch background. Children from families with lower net household income had 1.11 (95%CI=0.86-1.35) and 1.02 (95%CI=0.57-1.47) hours/week more computer use at 6 and 9 years than those from families with higher net household income. Children from families with lower maternal education level had 0.63 (95% CI=0.23-1.03) hours/week more outdoor exposure at 9 years, and 1.02 (95%CI=0.78-1.26) and 0.85 (95%CI=0.40-1.29) hours/week more computer use at respectively 6 and 9 years than those from families with higher maternal education level. No significant differences in outdoor exposure were identified for maternal education level at 6 years and net household income levels at 6 and 9 years (Fig A1-A2, Table A1).

Table 1. General characteristics

Generation R cohort (n=2643)	Age 6	Missing (%)	Age 9	Missing (%)
Age (±SD; years)	6.06±0.38	0.0	9.75±0.27	0.0
Sex (% ♀)	50.1	0.0		
Ethnic background (% Dutch)	62.8	0.1		
Myopia (%)	2.2	1.0	12.2	3.6
Axial length/corneal radius ratio (±SD)	2.87±0.07	0.0	2.97±0.09	0.0
Axial length (±SD; mm)	22.34±0.73	0.0	23.10±0.83	0.0
Maternal education (% low)	41.1	1.0		
Net household income (% low)	48.4	1.2	45.1	1.2
Outdoor exposure (±SD; hours/week)	11.38±7.61	19.9	7.39±5.12	5.1
Computer use (±SD; hours/week)	2.08±3.08	8.7	5.20±5.63	8.6

Myopia incidence between age 6 and 9 was higher in children with non-Dutch background, families with lower net household income and lower maternal education (OR=2.39, 95%CI=1.74-3.30; OR=1.52, 95%CI=1.10-2.09; OR=1.38, 95%CI=1.00-1.90; respectively) (Fig 1). axial length/corneal radius ratio change and axial elongation were greater in children with non-Dutch background (β=0.003, 95%CI=0.001-0.004 and β=0.019, 95%CI=0.012-0.027 respectively), and axial length/corneal radius ratio change was greater in children from families with lower household income (β=0.001, 95%CI=6.0E-5-0.002). No significant differences were identified for maternal education level. Adjusting for outdoor exposure, computer use and season of data collection at 6 years slightly decreased the associations (Table A2).

Children who gained access to a physical activity space had 7.43 hours/week outdoor exposure at age 9, while children who did not gain access had 7.25 hours/week outdoor exposure. However, living within 600 m of a newly introduced physical activity space was not significantly associated with outdoor exposure at age 9 (β=0.43 hours/week, 95%CI=-0.26-1.12) or change in outdoor exposure from age 6 to age 9 (β=0.08 hours/week, 95%CI=-1.12-1.28) (Table 2). Stratified analyses showed that children from families with lower maternal education had 8.26 hours/week outdoor exposure at age 9 if they lived within 600 m of a newly introduced physical activity space, and 7.33 hours/week if they lived further away than 600 m, resulting in 1.33 hours/week (95% CI=0.15-2.51) more outdoor exposure associated with gaining access to a physical activity space when adjusting for season of data collection, age, sex and ethnic background (Table 2).

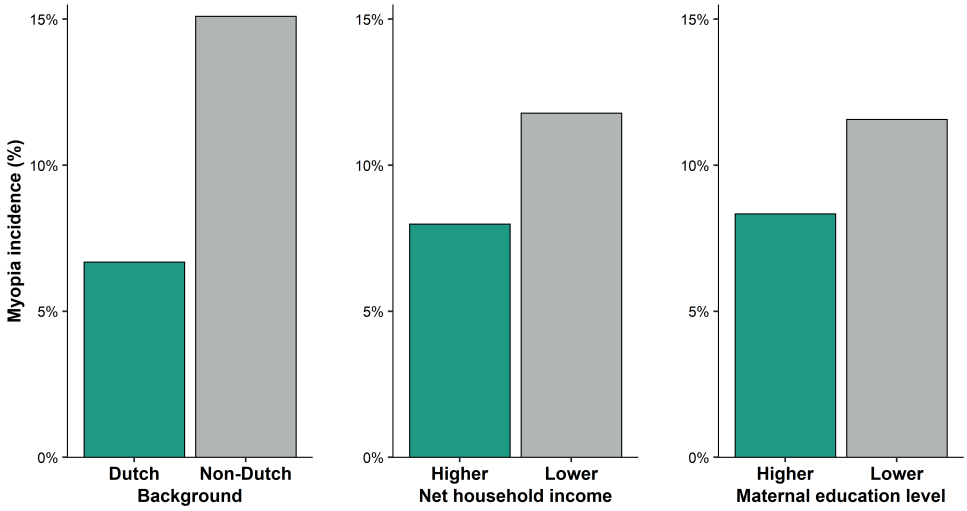

Fig 1. Bar chart depicting the proportion of children with incident myopia from 6 to 9 years, stratified by ethnic background (left), net household income at baseline (middle) and maternal education level (right).

Children who gained access to a physical activity space had 0.22 mm axial elongation per year, while children who did not gain access had 0.21 mm axial elongation per year. The fixed-effect model showed that the introduction of physical activity spaces within 600 m from home between the age of 6 and 9 had no effect on axial length/corneal radius ratio change (β=0.00 95% CI=-0.00-0.01) or axial elongation (β=0.03 mm/year 95%CI=-0.01-0.07). Adding the covariates household income and computer use to the model did not change the results, as well as stratified analyses by net household income, maternal education level and ethnic background (Table 3). Sensitivity analyses excluding myopic children at baseline, with buffer sizes of 400 m and 800 m, exclusion of children who lived less than 6 months within 600m of a new physical activity space, and exclusion of children who moved houses yielded similar results as the main analyses (Table A3).

Table 2. Longitudinal analyses of the introduction of physical activity spaces on outdoor exposure at age 9, and the change in outdoor exposure from 6 to 9 years, stratified by ethnic background, net household income at baseline and maternal education level.

		Outdoor exposure at age 9			Change in outdoor exposure	
	Intervention /control (n)	β (95% CI) (unit = hours/week)	P-value	Intervention/control (n)	β (95% CI) (unit = hours/week change)	P-value
All [a]	218/1779	0.429 (-0.262-1.120)	0.224	171/1455	0.080 (-1.118-1.278)	0.896
Ethnic background [b]						
Dutch	115/1234	0.274 (-0.648-1.197)	0.560	98/1057	0.149 (-1.369-1.667)	0.847
Non-Dutch	103/545	0.611 (-0.443-1.665)	0.256	73/398	0.156 (-1.832-2.144)	0.878
Net household income [a]						
Higher	104/1007	0.225 (-0.704-1.153)	0.635	85/855	-0.609 (-2.184-0.966)	0.448
Lower	113/754	0.783 (-0.259-1.824)	0.141	85/587	0.640 (-1.224-2.505)	0.500
Maternal education [a]						
Higher	123/1107	-0.262 (-1.117-0.594)	0.549	103/929	-0.928 (-2.358-0.501)	0.203
Lower	92/658	1.329 (0.150-2.508)	0.027	66/517	1.676 (-0.488-3.840)	0.129

[a] *Adjusted for season of data collection, age, sex and ethnic background.* [b] *Adjusted for season of data collection, age and sex.*

Table 3. The effect of the introduction of physical activity spaces on axial length/corneal radius ratio change and axial elongation using fixed-effects analyses stratified by ethnic background, net household income and maternal education

		axial length/corneal radius ratio change		Axial elongation	
	Intervention/control (n)	β (95% CI) (unit = 1 unit change/yr)	P-value	β (95% CI) (unit = mm/yr change)	P-value
Physical activity space [a]	230/1866	0.004 (-0.002-0.010)	0.164	0.030 (-0.012-0.073)	0.161
Physical activity space [b]	196/1580	0.002 (-0.004-0.008)	0.498	0.012 (-0.033-0.058)	0.599
Lower net household income		$-1.2E^{-4}$ (-0.005-0.005)	0.964	-0.007 (-0.043-0.030)	0.728
Computer use		$3.4E^{-4}$ ($-5.3E^{-5}$-$7.4E^{-4}$)	0.089	0.003 ($1.2E^{-4}$-0.006)	0.041
Subgroup analyses					
Ethnic background [b]					
Dutch	112/1135	-0.001 (-0.008-0.007)	0.805	-0.003 (-0.057-0.051)	0.916
Non-Dutch	84/443	0.003 (-0.009-0.015)	0.597	0.009 (-0.075-0.093)	0.834
Net household income [c]					
Higher	98/916	-0.003 (-0.012-0.005)	0.465	-0.015 (-0.077-0.047)	0.631
Lower	98/664	0.007 (-0.002-0.016)	0.130	0.037 (-0.029-0.104)	0.275
Maternal education [b]					
Higher	113/995	0.006 (-0.002-0.014)	0.118	0.038 (-0.020-0.097)	0.200
Lower	81/576	-0.004 (-0.014-0.006)	0.439	-0.022 (-0.094-0.050)	0.548

[a] Adjusted for age and season of data collection. [b] Adjusted for age, season of data collection, net household income and computer use. [c] Adjusted for age, season of data collection and computer use.

DISCUSSION

This study identified distributions of myopia, eye growth, outdoor exposure and computer use across socioeconomic groups, and investigated whether population health can be improved by physical activity spaces. We followed children who did not have a physical activity space in their neighbourhood at age 6, but gained access before the age of 9 years, and estimated the effect on eye growth. We found that myopia incidence was higher in children from socioeconomically disadvantaged families and in children with non-Dutch background. This difference could, in part, be explained by lifestyle factors. Computer use was higher in these children, while outdoor exposure was significantly lower in children with non-Dutch background. Children from families with lower educated mothers who became exposed to new physical activity spaces in their neighbourhood had 1.33 hours/week more outdoor exposure than those without access to physical activity spaces. This increase was not enough to significantly diminish eye growth.

Strength and limitations

Strengths of the study were the population-based prospective cohort design, the large sample size, the comprehensive set of socio-economic determinants, and the innovative use of an experimental approach to analyse observational data.[25] This approach enabled removal of the effects of time-invariant causes, even those unmeasured, such as people's choice to live in a neighbourhood with many opportunities for children to play outdoors.[22] As fixed-effects models do not account for time-variant factors, we controlled for age, change in net household income, and change in computer use. To ensure that we addressed long-term physical activity exposure, we performed sensitivity analyses excluding children who were only exposed <6 months. The limitations included a relatively large amount of missing data on outdoor exposure, the use of questionnaires to determine outdoor exposure and computer use, and the lack of information on the play-time spent at physical activity spaces.

Traditionally, high education and urbanization were the strongest risk factors for myopia all over the world.[1, 26] Excessive amounts of near work and lack of outdoor exposure may explain this association.[26, 27] In Asia, particularly children from higher educated families attending private or cram schools were more often myopic.[28, 29] In Europe, this trend might be to be changing. In the E^3 consortium, the association with education was strong in the older age groups, but became less apparent in younger age groups,[1] recent studies from Ireland and Germany did not find any association between socioeconomic status and myopia in children,[14, 30] and previous results from Generation R data at age 6 years showed that low family income and low maternal education predisposed to myopia prevalence.[11] This suggests a shift in myopia risk from children from highly educated families to children from socioeconomically

disadvantaged families in Europe. Our current data from children at age 9 reinforce this notion, as newly developed myopia occurred more often in children from low household income, low maternal education, and children from non-Dutch families had a larger change in AL/CR and axial elongation. Health problems may shift from higher towards lower socioeconomic groups, in a different tempo between countries. This is a known phenomenon, illustrated well by for example a social transition in smoking and higher body mass index from the more affluent to socioeconomically disadvantaged members of society.[31] Several reasons may explain the reversed association between socio-economic factors and myopia in our study as compared to previous studies. First, only children living in the city of Rotterdam were included in the analyses thereby not influenced by living environment (urban versus rural areas). As higher educated people more often live in urban areas, previous studies on socio-economic position and myopia may have been partly confounded by urbanisation.[28, 29] Second, the effect of education is not visible yet in 6 and 9 year old children as they go to generally similar primary schools, in contrast to studies focussing on education and myopia in adults or adolescents.[26, 32] Conflicting results have been reported about household income and myopia in recently published studies.[33, 34] Third, children from higher socio-economic position and native Dutch children more often participate in sports than children from lower socio-economic position and ethnic minorities in Generation R which may result in less myopia in these groups.[12] Fourth, academic pressure from parents may be stronger in East Asian countries than in European countries as illustrated by the high prevalence of cram school attendance in East Asia.[35]

Non-Dutch background was the most pronounced association with myopia at early age in our study, and was also observed for axial elongation and change in AL/CR. From the 1960s onwards, the immigration number increased because of the recruitment of low-skilled guest workers and refugees, and later because of family reunification.[36] In our study, parents from families with non-Dutch background were mostly from Europe or Africa, only a small proportion (3.3%) was from Asia. After adjustment for outdoor exposure, computer use and season of data collection, the association between ethnic background and myopia became slightly less strong. Studies on myopia in African adults reported low prevalence,[37] we therefore believe that our findings are not explained by a different genetic background. Residual confounding of environmental factors may be more likely, especially because mothers with non-Dutch background were more often lower educated and families with non-Dutch background more often had a lower household income.

Environmental factors are considered the most likely cause of the worldwide increased myopia incidence.[38] Lack of outdoor exposure is an established risk factor, and has been a target for successful intervention studies.[6, 7] There is also growing evidence for increased use of computers and handheld screens.[39, 40] In this study, we found that children from families with low household income, low maternal education, and non-Dutch background had ~1

hours/week more computer use than their peers. This may explain, in part, the socioeconomic and ethnic background inequalities in myopia incidence in our cohort.[11] Other studies also reported that increased sedentary behaviour, computer and hand held device use and lack of outdoor exposure is more common among socioeconomically disadvantaged families.[11, 12, 41] Parents from these families may have less stricter rules concerning non-educational screen time, which could explain the difference.[42]

Two hours per day of outdoor exposure is currently recommended to prevent children from myopia or myopia progression.[43] Most of the children in our cohort did not meet this advice, especially when they reached the age of 9 years and those with non-Dutch background. Previous research showed that children from socioeconomically disadvantaged families or ethnic minorities less often participate in sports and outdoor play.[12, 44] We therefore performed our analyses in the whole group and in several subgroups. The introduction of new physical activity spaces within the neighbourhood was associated with 0.19 hours/day extra outdoor exposure among children from families with lower maternal education; outdoor exposure was 1.04 hours/day in those without physical activity space and 1.19 hours/day in those who gained access to a new physical activity space. No differences in outdoor exposure were identified in the other subgroups. Hence, no differences in eye growth were identified. School-based randomized controlled trials showed that at least 0.67 hours/day extra outdoor exposure was needed to prevent children from myopia.[6, 7] Increased surrounding greenness was associated with 0.13 hours/week increased time spent playing in green spaces and a reduced risk of incident spectacle use in the BREATHE study.[46] A recent review concluded that the presence of a safe and green neighbourhood was positively associated with outdoor play.[44] Increased surrounding greenness may be more effective against myopia prevention than the physical activity spaces in our study since the physical activity spaces were mainly placed in deprived and perhaps less safe neighbourhoods. Previous research showed that playground use was higher at Krajicek physical activity spaces as compared to regular playgrounds in deprived areas.[16] Benefits of Krajicek and Cruyff spaces are the supervision from community organisations and organised events. The introduction of these physical activity spaces may have led to a shift from another outdoor play location rather than an increase in outdoor play. Unfortunately, we did not have information about the children's outdoor play locations to investigate this. More research on neighbourhood interventions that are effective in increasing outdoor exposure is needed as indoor activities such as screen time behaviour in children is becoming extremely popular.[47]

In conclusion, the results of our study showed that myopia incidence is more common among primary school aged children from socioeconomically disadvantaged families, which may be partly explained by differences in outdoor exposure and computer use. physical activity spaces do not appear to increase outdoor exposure to such extent that it reduces eye growth

in all children, although subgroups may benefit. More far stretching strategies are needed to increase outdoor play, reduce non-educational screen time in school-aged children in the entire population, and consequently reduce risk of myopia and myopia progression.

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SUPPLEMENTS

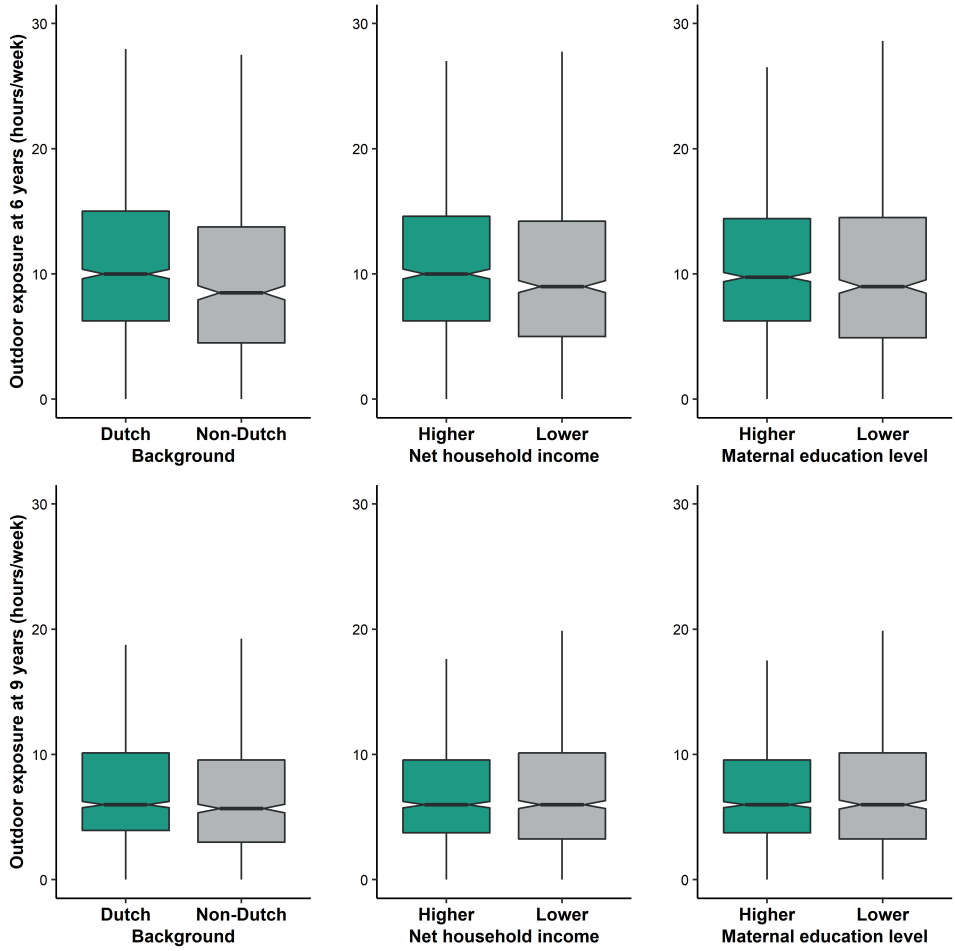

Fig A1. Boxplots depicting outdoor exposure at 6 and 9 in hours per week, stratified by ethnic background, net household income at baseline and maternal education level. The box represents the interquartile range (the 25th and 75th percentiles) and the horizontal line is drawn at the median, the whiskers indicate -1.5*25th percentile and -1.5*75th percentile.

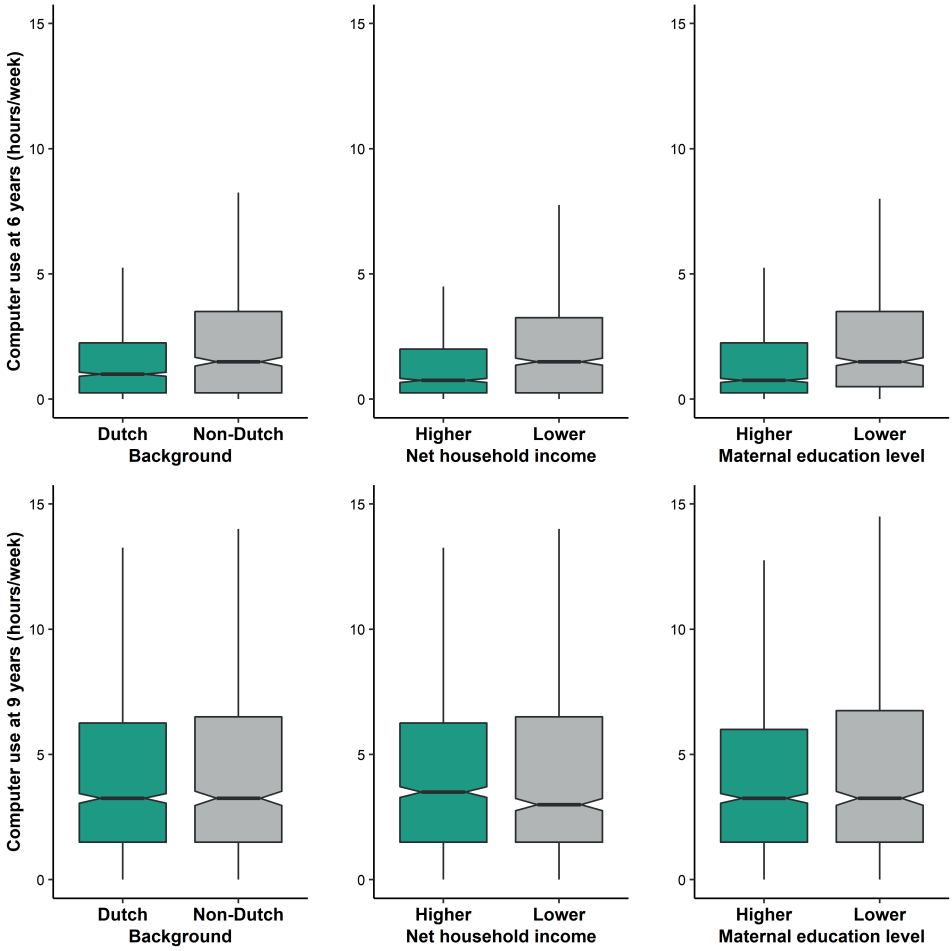

Fig A2. Boxplots depicting computer use at 6 and 9 in hours per week, stratified by ethnic background, net household income at baseline and maternal education level. The box represents the interquartile range (the 25th and 75th percentiles) and the horizontal line is drawn at the median, the whiskers indicate -1.5*25th percentile and -1.5*75th percentile.

Table A1. Cross-sectional analyses of ethnicity, net household income and maternal education level on outdoor exposure and computer use at age 6 and 9 years.

	Number of participants (n) [a]	Outdoor exposure at 6 years		Number of participants (n) [a]	Outdoor exposure at 9 years	
		β (95% CI) (unit = hours/week)	P-value		β (95% CI) (unit = hours/week)	P-value
Non-Dutch ethnic background [b]	1414/700	-1.46 (-2.10- -0.82)	$7.9E^{-6}$	1601/905	-0.55 (-0.96- -0.14)	0.009
Lower net household income [b]	1137/959	-0.23 (-0.83-0.38)	0.466	1303/1177	0.23 (-0.16-0.62)	0.248
Lower maternal education [b]	1284/819	0.37 (-0.26-0.99)	0.250	1487/998	0.63 (0.23-1.03)	0.002
		Computer use at 6 years			**Computer use at 9 years**	
		β (95% CI) (unit = hours/week)	P-value		β (95% CI) (unit = hours/week)	P-value
Non-Dutch ethnic background [b]	1565/847	0.97 (0.72-1.22)	$5.1E^{14}$	1578/836	1.33 (0.87-1.80)	$2.3E^{-8}$
Lower net household income [b]	1256/1131	1.02 (0.78-1.26)	$5.2E^{-17}$	1261/1127	0.85 (0.40-1.29)	$1.9E^{-4}$
Lower maternal education [b]	1431/964	1.11 (0.86-1.35)	$1.7E^{-18}$	1435/966	1.02 (0.57-1.47)	$8.2E^{-6}$

[a] *Numbers represent Dutch/non-Dutch, higher net household income/lower net household income and higher maternal education level/lower maternal education level.* [b] *Adjusted for season of data collection, age and sex.*

Table A2. Longitudinal analyses of ethnic background, net household income and maternal education level on myopia incidence, axial length/corneal radius ratio change and axial elongation.

	Number of participants (n) [a]	Myopia incidence		Number of participants (n) [a]	Axial length/corneal radius ratio change		Number of participants (n) [a]	Axial elongation	
		OR (95% CI)	P-value		β (95% CI)	P-value		β (95% CI)	P-value
Non-Dutch background [b]	1271/596	2.39 (1.74 – 3.30)	$9.2E^{-8}$	1345/651	0.003 (0.001 – 0.004)	$3.4E^{-6}$	1345/651	0.019 (0.012 – 0.027)	$1.1E^{-6}$
Non-Dutch background [c]	1271/596	2.20 (1.59 – 3.07)	$2.4E^{-6}$	1345/651	0.002 (0.001 – 0.003)	$3.7E^{-5}$	1345/651	0.018 (0.010 – 0.026)	$7.4E^{-6}$
Lower net household income [b]	1010/840	1.52 (1.10 – 2.09)	.010	1075/903	0.001 ($6.0E^{-5}$ – 0.002)	0.038	1075/903	0.006 (-0.001 – 0.014)	.091
Lower net household income [c]	1010/840	1.44 (1.04 – 2.00)	.027	1075/903	$9.2E^{-4}$ ($-1.1E^{-4}$ – 0.002)	0.080	1075/903	0.006 (-0.002 – 0.013)	.140
Lower maternal education [b]	1148/710	1.38 (1.00 – 1.90)	.048	1213/772	$5.6E^{-4}$ ($-4.8E^{-4}$ – 0.002)	0.293	1213/772	0.002 (-0.005 – 0.010)	.585
Lower maternal education [c]	1148/710	1.36 (0.97 – 1.89)	.069	1213/772	$4.9E^{-4}$ ($-5.7E^{-4}$ – 0.002)	0.360	1213/772	0.002 (-0.005 – 0.010)	.565

[a] Numbers represent Dutch/non-Dutch, higher net household income/lower net household income and higher maternal education level/lower maternal education level. [b] Adjusted for age and sex. [c] Additionally adjusted for outdoor exposure, computer use and season of data collection at 6 years.

Table A3. The effect of the introduction of PA spaces on AL/CR change and axial elongation using fixed-effects excluding baseline myopia, using buffer zones of 400 and 800 meters, excluding children who lived less than 6 months near a physical activity space and excluding children who moved houses within the study period.

		Axial length/corneal radius ratio change		Axial elongation	
	Intervention/ control (n)	β (95% CI) (unit = 1 unit change/year)	P-value	β (95% CI) (unit = mm/year change)	P-value
No baseline myopia [a]	193/1525	0.003 (-0.003-0.009)	0.364	0.017 (-0.027-0.060)	0.452
Physical activity space <400m [b]	82/1694	0.004 (-0.006-0.013)	0.418	0.016 (-0.052-0.084)	0.640
Physical activity space <800m [c]	433/1343	0.004 (-0.002-0.009)	0.160	0.020 (-0.019-0.058)	0.313
Novelty effect [d]	169/1580	0.002 (-0.005-0.009)	0.519	0.012 (-0.037-0.060)	0.637
Without movers [e]	146/1434	0.001 (-0.006-0.008)	0.767	0.006 (-0.046-0.058)	0.830

[a] *Excluding children who were already myopic at 6 years old.*
[b] *Using buffer zones of 400m from home.*
[c] *Using buffer zones of 800m from home.*
[d] *Excluding children of which the data was collected within 6 months after being exposed to a dedicated physical activity space.*
[d] *Excluding children who moved houses within the study period.*
All analyses are adjusted for age, season of data collection, net household income, and computer use.

Part V

Lifestyle influence on genetic drivers

9

Interaction between lifestyle and genetic susceptibility in myopia: the Generation R study

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ABSTRACT

Myopia is a refractive error of the eye caused by a complex interplay between nature and nurture. The aim of this study was to investigate whether environmental risk factors can influence the genetic effect in children developing myopia. A total of 3422 children participating in the birth-cohort study Generation R underwent an extensive eye examination at 9 years with measurements of refractive error and axial length corneal radius ratio (AL/CR). Environmental risk factors were evaluated using a questionnaire, and environmental risk scores (ERS) were calculated using backward regression analyses. Genetic risk scores (GRS) were calculated based on all currently known risk variants for myopia. Gene-environment interaction (GxE) was investigated using linear and logistic regression analyses. The predictive value of GxE and parental myopia was estimated using receiver operating characteristic curves. Myopia prevalence was 12%. Both GRS ($P<0.01$) and ERS ($P<0.01$) were significantly associated with myopia and AL/CR, as was GxE interaction ($P<0.01$ for myopia; $P=0.07$ for AL/CR). The predictive value of parental myopia was 0.67 (95% CI 0.65-0.70), similar to the values of GRS (0.67; 95% CI 0.64-0.70; $P=0.98$) and ERS (0.69; 95% CI 0.66-0.72; $P=0.98$). Adding GxE interaction significantly improved the predictive value to 0.73 (95% CI 0.70-0.75; $P<0.01$). This study provides evidence that nature and nurture are equally important for myopia and AL/CR; however, the combination has the strongest influence. Since myopia genes are common in the population, adjustment of lifestyle should be a major focus in the prevention of myopia.

INTRODUCTION

Myopia is the most common eye disorder in developed countries. Around 50% of young adults in Europe and up to 83% of the Chinese university students have myopia.[1,2] The global myopia prevalence is rising and expected to increase from one in three persons in 2000 to half of the worldwide population in 2050.[3] Myopia is caused by an axial elongation of the eye accompanied by structural changes of the retina and choroid. Although myopia can be optically corrected, it is associated with an increased risk of visual impairment and blindness later in life due to retinal complications such as myopic macular degeneration, cataract and glaucoma.[4] A higher degree of myopia results in an earlier onset of retinal complications.[5]

Myopia is caused by a complex interplay between nature and nurture.[6] Recently, large genome-wide association studies have identified 161 independent loci for refractive error,[7] which explain 8% of the variance of spherical equivalent in adults and can discriminate myopia from hyperopia with a 0.77 accuracy.[7,8] Established environmental risk factors that have been associated with myopia include extended near work and minimal outdoor exposure,[9-11] and lifestyle in childhood is most likely the major cause of the rapid rising prevalence. Whether lifestyle can alter the outcome of a genetic susceptibility for myopia is currently unsettled. Several studies in adults have demonstrated gene-environment interactions for refractive error, in particular with education.[12-15] However, whether this reflects a certain lifestyle in childhood is unclear and GxE interaction studies in children have been limited.[13, 14, 16, 17]

Children with an early onset of myopia are most likely to develop high myopia.[18, 19] Postponing myopia onset or, even better, preventing the onset can be achieved by lifestyle factors, such as spending many hours outdoors.[20, 21] As changing habits is extremely difficult,[22] knowledge on susceptibility may help children at risk to adhere lifestyle advice. This knowledge may be acquired by assessing parental myopia or calculating a genetic risk score when DNA analysis is feasible.[7, 8, 17, 23] Whether the latter has additional value is currently unknown.

In the Generation R birth cohort, we previously created a prediction model for myopia based on time spent outdoors, sports participation, number of books read per week, time spent reading, parental myopia, and ethnicity.[24] In the current analysis, we implemented known genetic factors to study gene-environment interactions using genetic and environmental risk scores. We also investigated the relationship between parental myopia and genetic and environmental factors and assessed the predictive value of these variables to identify children at risk for early onset myopia.

METHODS

Study population: Generation R

Generation R is a population-based prospective cohort of 9,778 pregnant women and their children who were born between April 2002 and January 2006 in Rotterdam, The Netherlands. The exact methodology of the Generation R study has been described elsewhere.[25, 26] Children were invited to the research center at the age 9 years. Of the initial cohort, 5862 (60%) children participated at the age of 9 years. Genetic data was available for 5731 children, and 3422 of them received eye measurements (58%). The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam (MEC 217.595/2002/20), and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Eye measurements

Automated cycloplegic refraction was performed in a random sample of children (42%). Two drops (three in case of dark irises) of cyclopentolate (1%) with 5 minutes interval were dispensed at least 30 minutes before refractive error measurement. Pupil diameter was ≥6 mm at the time of measurement. Children with a visual acuity of more than 0.1 logarithm of the minimum angle of resolution at a 3-m distance by means of the Early Treatment Diabetic Retinopathy Study method in at least 1 eye or children with an ophthalmologic history were referred to an ophthalmologist or orthoptist to identify myopia.[27] Children with visual acuity of 0.1 logarithm of the minimum angle of resolution or less or no glasses or ophthalmic history were classified as non-myopic.[28, 29] Spherical equivalent (SER) was calculated as the sum of the full spherical value and half of the cylindrical value. Myopia was defined as SER ≤-0.50 dioptre in at least one eye. Since SER was not available for the whole sample, the axial length/corneal radius (AL/CR) ratio was used as a proxy for refractive error. Ocular biometry was measured by Zeiss IOL-master 500 (Carl Zeiss MEDITEC IOL-master, Jena, Germany). For axial length (AL) five measurements per eye were averaged to mean AL. Three measurements of corneal radius (K1 and K2) were taken of both eyes, and mean corneal radius was calculated (CR). Mean AL/CR ratio was calculated by dividing AL (mm) by CR (mm) for both eyes, divided by two.

Environmental variables

Environmental variables were measured using a questionnaire filled in by the parents when the child was 9 years old. For outdoor exposure, the questions “how many days per week does your child play outside” and “how long does your child approximately play outside per day” were asked. Mean daily outdoor exposure was calculated by multiplying the number of days by time in minutes divided by seven. Walking or cycling to and from school was processed similarly. Outdoor exposure was calculated as the sum of playing outside and walking or

cycling to and from school. For computer use and watching television, the question "how much time does your child use the computer/watch television in the morning/afternoon/evening" was asked for weekdays and weekend days separately. Mean daily computer use and watching television was calculated by dividing the total time per week by seven. Time spent reading was asked per week (never, <5 hours/week, 5-10 hours/week, 11-15 hours/week or >15 hours/week), number of books read per week (<1 or 1≥ per week) and reading distance was asked and categorised in <30 cm or ≥30 cm. For parental myopia, 0, 1 or 2 myopic parents was registered by questionnaire.

Environmental risk score

Outdoor exposure, books per week, computer use, reading time and watching television were standardized into a mean of 0 en standard deviation of 1. A multivariate regression model including reading distance, outdoor exposure, number of books per week, computer use, time reading and watching television and interaction effects between them were tested. Backward linear regression analyses were performed until the final model only included significant environmental risk factors (P<0.05). Environmental risk scores (ERS) were computed for each individual using the beta-coefficients of the final multivariate regression model multiplied by the standardized values of the risk factors.

Genotyping and quality control

Genotyping and quality control were performed as described in Medina-Gomez C et al.[30] In summary, blood samples were taken from cord blood at birth or venepuncture at the age of 6 years during their visit at the research center. Genotyping was performed with the Illumina HumanHap 610 (at birth) or 660 (at age 6 years) Quad Chips. Quality control procedures were performed using PLINK.[31] Filters were used for marker call rate (calling <0.2 – <0.05), minor allele frequency (MAF) ≥1%, and deviation from Hardy-Weinberg equilibrium ($P<10^{-6}$). Additional quality control steps included checks for excess heterozygosity, sex mismatch, relatedness and missing data.

Genetic risk scores

GRS were computed using the summary statistics from a large meta-analysis.[7] We incorporated genetic variants with minor allele frequency greater than 1% and an imputation information score greater than 0.5 or minimac R^2 greater than 0.8. P-value based clumping was performed in PLINK using one genetic variant per linkage disequilibrium region.[32] Genetic variants with an r-squared smaller than 0.2 and a physical-distance over 500 kb, excluding the major histocompatibility complex region, were selected. For each individual, GRS values were calculated in PLINK across the following strata of P-value thresholds: 5.0 × 10–8, 5.0 × 10–7, 5.0 × 10–6, 5.0 × 10–5, 5.0 × 10–4, 0.005, 0.01, 0.05, 0.1, 0.5, 0.8 and 1.0. The proportion

of variance of AL/CR explained by each GRS model was calculated as the difference in the r-squared between two linear regression models: one in which AL/CR was regressed on age, sex and the first ten principal components, and the other also including the GRS as an additional covariate.

Gene-environment interaction and correlation

Gene-environment interaction (GxE) is defined as a different effect of a genotype on disease risk in persons with different environmental exposures. In contrast, gene-environment correlation (rGE) refers to the association of different genotypes on environments, in other words individuals are selectively exposed to different environments based on their genetics. Presence of rGE could confound GxE interaction analyses and was therefore assessed.[33, 34]

Statistical analyses

Myopia yes/no was considered the dichotomous outcome variable; AL/CR was used as the continuous outcome. Association analyses were based on cross-sectional data, and prevalence odds ratios were used to represent risk of myopia. Participants with myopia were compared to controls with respect to age, sex, ethnicity, AL/CR and environmental factors using t-tests for continuous variables and chi-square tests for binary variables. Missing information on the covariates varied between 0 and 36% (Table 1). Multiple imputation procedures were performed to replace missing covariates for the most likely values to avoid bias in the analyses using Multivariate Imputations by Chained Equations (MICE).[35] GRS and ERS were computed using linear regression analyses and the proportion of phenotypic variance of AL/CR explained was computed using the R^2 minus the reference model including age, sex and ethnicity and first ten principal components. Linear regression (for AL/CR) and logistic (for myopia) analyses were performed to test for GxE interactions and rGE correlations, adjusted for age, sex and first ten principal components. Sensitivity analyses were performed for GxE interaction restricted to European children to capture ethnicity-related differences in lifestyle risk factors. The predictive value (area under the receiver operating characteristic curve, AUC) of myopia versus no myopia was calculated for parental myopia, ERS, GRS and combinations of them using pROC package in R.[36] All analyses were performed in SPSS software version 24.0 and R statistical software version 1.1.456.[37, 38]

RESULTS

Data from 3422 children entered the analyses and a myopia prevalence of 12% was calculated (Table 1). Children with myopia were more often non-European, had more often a short reading distance, spent more time on reading, had a tendency towards spending less time outdoors and had more often 1 of 2 myopic parents than their peers (Table 1). A backward

regression model showed that outdoor exposure (P=0.03), reading distance (P<0.01) and number of books read per week (P<0.01) were significantly associated with AL/CR (Table 2). No significant interactions were found between the environmental variables. ERS explained 1.1% of the variance of AL/CR and 2.1% of myopia (Table 3).

Table 1. General characteristics

Generation R cohort (N=3422)a		Missing (%)	Myopia (N=391)	No myopia (N=2900)	P-valueb
Myopia (%)	11.9	4	-	-	-
Age (±SD; years)	9.79 (0.34)	0	9.82 (0.36)	9.79 (0.33)	0.05
Sex (% ♀)	50.8	0	51	51	0.41
Ethnicity (% EUR)	87.8	0	78.0	89.3	<0.01
AL/CR (±SD)	2.97 (0.10)	1	3.11 (0.10)	2.95 (0.08)	<0.01
Reading distance (% <30cm)	49.1	36	66.9	46.6	<0.01
Outdoor exposure (hr/day)	1.09 (0.75)	17	1.02 (0.73)	1.09 (0.75)	0.10
Books per week (% >1)	44.6	32	57.3	43.0	<0.01
Computer use (hr/day)	0.72 (0.78)	20	0.79 (0.90)	0.72 (0.77)	0.16
Time reading (% >5 hr/wk)	38.3	32	46.3	37.1	<0.01
Watching television (hr/day)	1.70 (1.19)	20	1.78 (1.38)	1.69 (1.15)	0.25
Parental myopia (% 1 and % 2)	40.2 15.4	33	44.2 26.5	39.6 14.1	<0.01 <0.01

a 3406 participants with complete data on AL/CR and 3291 participants with complete data on myopia. Total amount of participants is 3422. b P-values are corrected for age and sex. SD = standard deviation; EUR = European; AL/CR = axial length corneal curvature ratio; hr/day = average hours per day. Missing information on the variables were imputed using multiple imputations, with the exemption of myopia and AL/CR.

Table 2. Full and backward regression model with environmental predictors for AL/CR

	Full regression model			Backward regression model		
N= 3406	Estimate	SE	P-value	Estimate	SE	P-value
Outdoor exposurea	-0.004	0.002	0.03	-0.004	0.002	0.03
Reading timea	0.003	0.002	0.16	-	-	-
Reading distancea	-0.007	0.002	<0.01	-0.007	0.002	<0.01
Watching televisiona	0.000	0.002	0.86	-	-	-
Computer usea	0.002	0.002	0.30	-	-	-
Books per weeka	0.005	0.002	0.05	0.006	0.002	<0.01

a Environmental variables are standardized and adjusted for age, sex and ethnicity. Estimate = Beta-coefficient; SE = standard error.

GxE interaction was borderline significant for AL/CR (P=0.07) and significant for myopia (P<0.01), indicating that the effect of GRS on AL/CR and myopia increased within higher levels of ERS (Table 3). Analyses restricted to children with European ancestry showed similar results (P=0.09 for AL/CR and P<0.01 for myopia), indicating that ethnicity-related differences in lifestyle did not bias the GxE results. Figure 1 shows that the risk of myopia among subjects who were in the highest tertiles for GRS and ERS was increased (ORcombined = 1.23; 95% CI 1.18-1.29), and was higher than multiplication of the risks among individuals with only one of these factors (ORcombined for high GRS = 1.04; 95% CI 1.00-1.09; ORcombined for high ERS = 1.06; 95% CI 1.01-1.11) (Table S3, Figure 1).

Table 3. Variance explained by environmental risk score (ERS), genetic risk score (GRS) and the interaction term (ERS x GRS) for AL/CR and myopia

AL/CR (N=3406)	Variable	Estimate	SE	P-value	Variance explained (%) f
Reference model[a]	NA	NA	NA	NA	1.9
ERS model[b]	ERS	0.010	0.002	<0.01	3.0
GRS model[c]	GRS	0.017	0.002	<0.01	5.0
ERS + GRS model[d]	ERS	0.010	0.002	<0.01	6.0
	GRS	0.017	0.002	<0.01	
ERS x GRS model[e]	ERS	0.010	0.002	<0.01	6.1
	GRS	0.017	0.002	<0.01	
	ERS x GRS	0.004	0.002	0.07	
Myopia (N=3291)	**Variable**	**Odds Ratio**	**95% CI**	**P-value**	**Variance explained (%) f**
Reference model[a]	NA	NA	NA	NA	1.7
ERS model[b]	ERS	1.048	1.035-1.061	<0.01	3.8
GRS model[c]	GRS	1.045	1.033-1.056	<0.01	4.3
ERS + GRS model[d]	ERS	1.046	1.033-1.058	<0.01	6.2
	GRS	1.043	1.032-1.055	<0.01	
ERS x GRS model[e]	ERS	1.046	1.033-1.058	<0.01	6.7
	GRS	1.043	1.032-1.055	<0.01	
	ERS x GRS	1.024	1.008-1.039	<0.01	

*a Reference model includes age, sex and ethnicity. b ERS adjusted for age, sex and ethnicity. c GRS adjusted for age, sex and first 10 principal components. d ERS and GRS adjusted for age, sex and first 10 principal components. e ERS, GRS and the interaction term ERS x GRS adjusted for age, sex and first 10 principal components. f Explained variance is computed as: NagelkerkeR² * 100%. AL/CR = axial length corneal curvature ratio; ERS = Environmental risk score; GRS = Genetic risk score; Estimate = Beta-coefficient; SE = standard error; NA = not applicable; 95% CI = 95% Confidence Interval.*

A total of 243,261 genetic variants were available for the GRS, which ranged from P-value threshold 5.00E-08 (including 175 variants) to P-value threshold 1 (including 243,261 variants). The highest proportion of the variance explained by genetic variants was the stratum

of GRS with P-value threshold 0.1 (Table S1), which included 65,426 variants for AL/CR (4.4%) and myopia (2.3%). Significant rGE was found from P-value threshold 5.00E-05 onwards (≥784 variants) (β=0.047 to β=0.062, P<0.01 to P=0.03), meaning this could bias the results of GxE analyses (Table S2). Therefore, GRS including only 175 genome-wide significant variants were used for GxE analyses.

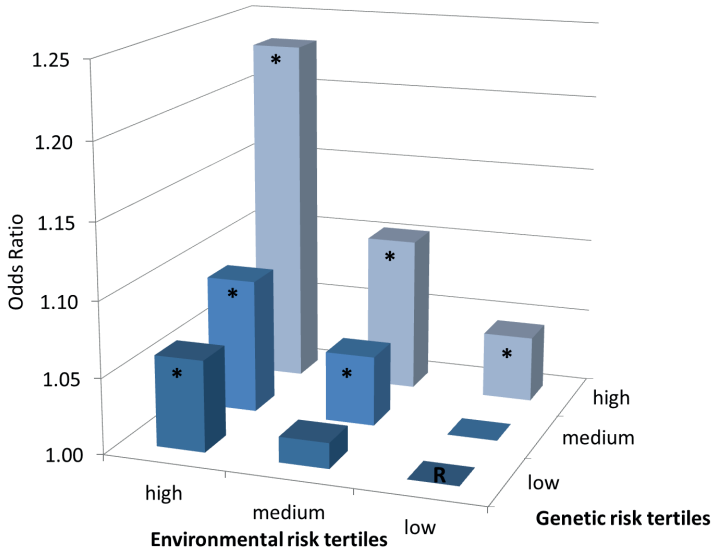

Figure 1. Odds Ratio for myopia per GRS and ERS tertiles
*The age-, sex-, and principal components-adjusted odds ratio for myopia versus no myopia for environmental risk score tertiles and genetic risk score tertiles. The group with low environmental risk and low genetic risk served as the reference. * = significant OR compared to the reference group. OR = odds ratio, R = reference (i.e. OR 1.0).*

Table 4. Association between parental myopia and environmental risk score and genetic risk score

N=3422	Estimate	SE	P-value
ERS model[a]			
1 myopic parent	0.083	0.043	0.06
2 myopic parents	0.160	0.067	0.02
GRS model[b]			
1 myopic parent	0.225	0.044	<0.01
2 myopic parents	0.226	0.059	<0.01

a ERS adjusted for age, sex and ethnicity. b GRS adjusted for age, sex and first 10 principal components. ERS = Environmental risk score; GRS = Genetic risk score; Estimate = Beta-coefficient; SE = standard error.

Parental myopia was associated with both ERS (1 myopic parent: β=0.083, P=0.06; 2 myopic parents: β=0.160, P<0.01) and GRS (1 myopic parent: β=0.225, P= <0.01; 2 myopic parents: β=0.226, P<0.01), indicating that parental myopia comprises shared genetic and environmental factors (Table 4). The prevalence of myopia was 8.3% among children without myopic parents, 13.7% among children with 1 myopic parent, and 18.4% among children with 2 myopic parents (P trend <0.01). The predictive value (calculated as area under the receiver operating characteristic curve, AUC) for parental myopia was 0.67 (95% CI 0.65-0.70), which was not statistically different from the AUC for GRS (0.67; 95% CI 0.64-0.70; P=0.98) or for ERS (0.69; 95% CI 0.66-0.72; P=0.98). Combining parental myopia with GRS, ERS or GxE, improved the AUC to 0.70, 0.71, and 0.73 respectively (95% CI 0.67-0.73; P<0.01; 95% CI 0.68-0.73; P<0.01; 95% CI 0.70-0.75; P<0.01; Table 5).

Table 5. The predictive value (area under the receiver operating characteristic curve, AUC) of myopia versus no myopia

N=3291	AUC	95% CI	P-value[c]
Reference model[a]	0.63	0.60-0.66	<0.01
Parental myopia model[b]	0.67	0.65-0.70	-
GRS model[b]	0.67	0.64-0.70	0.78
ERS model[b]	0.69	0.66-0.72	0.98
GRS + parental myopia[b]	0.70	0.67-0.73	<0.01
ERS + parental myopia[b]	0.71	0.68-0.73	<0.01
ERS*GRS + parental myopia[b]	0.73	0.70-0.75	<0.01

a Reference model includes age, sex and first ten principal components. b Adjusted for age, sex and first ten principal components. c In comparison with the parental myopia model. ERS = Environmental risk score; GRS = Genetic risk score; AUC = area under de curve; 95% CI = 95% Confidence Interval.

DISCUSSION

Within our sample of Dutch children aged 9 years old, we found a myopia prevalence of 12%. The risk profile of children who were myopic included high genetic load (high GRS) for myopia and AL/CR, and environmental risk factors such as short reading distance, reading >1 book per week and <7 hours outdoor exposure per week. Children with a high GRS in combination with high ERS had a greater risk of myopia compared to children with only one of these factors, and this gene-environment interaction was statistically significant. Parental myopia was associated with ERS as well as PRS, indicating shared genetic and shared environmental factors. The predictive value of parental myopia, ERS, and GRS, and GxE combined was 0.73, significantly higher than models with only one of these variables.

Our study had strengths and limitations. Strengths included the large dataset, the extensive evaluation of lifestyle, the thorough genetic screen, and the young age of participants which enabled identification of determinants close to the onset of the trait. Our analyses were performed using continuous variables, which benefitted statistical power for the GxE investigation. Among limitations are the cross-sectional design of our study and the self-report of the environmental risk factors. Future studies incorporating real-time measurements of near work and outdoor exposure will facilitate more accurate evaluation.

Our study investigated the effect of GRS and ERS on myopia outcomes as single exposures as well as the combination. The GRS in this study was based on the stratum of genetic variants which best explained AL/CR and myopia (4.4% and 2.3%, respectively). Our former calculation was based on only 39 SNPs, and explained a much lower variance for AL/CR (0.7% at age 6 years and 3.7% in adults).[39] Other studies found 0.6% to 1.1% and 2.3% to 2.6% of the variance explained for spherical equivalent at age 7 and 15 years, respectively.[17, 40]

With respect to ERS, we found significant associations for outdoor exposure, books per week, and reading distance with AL/CR. Number of books per week was highly correlated with reading time, and the association with the latter disappeared when both variables were included in the model. Watching television was not associated, and computer use appeared weakly associated but failed to reach statistical significance. This is in line with previous findings.[9, 11, 24, 41] Despite the low proportion of variance explained by ERS (2.1% of myopia and 1.1% AL/CR), its predictive value was 0.69, comparable to earlier lifestyle studies in children.[23, 24]

Lifestyle can be genetically determined, and vice versa, familial risk can be driven by environmental factors. We tested the association between GRS and ERS, and found a significant correlation when 784 or more genetic variants (P-value threshold 5.00E-05, table S2) were included in the GRS. This would imply that lifestyle may be partly genetically determined by variants involved in myopia, i.e. ERS may be a mediator in the association between GRS and myopia outcomes.[34] A recently published paper provided evidence for a genetic correlation between myopia and IQ, and IQ may influence behaviour leading to more near work and less outdoor exposure.[42] This correlation could confound a true GxE association, therefore, we studied the GRS stratum that did not associate with ERS. The results of the GxE analyses show that the effect of GRS on myopia outcomes is influenced by environmental exposure.

Few GxE interactions for myopia were discovered in previous studies. Verhoeven et al. revealed a biological interaction between education and a GRS including 26 genetic variants for myopia.[12] A genome-environment wide interaction study (GEWIS) found interaction between three genetic markers and education in adult Asian populations.[15] A GEWIS for interaction

with near work hinted towards an interaction with lifestyle, but the GRS failed to find evidence for interaction with near work or outdoor exposure.[15, 17] Different from our study is that we created a continuous environmental risk score and genetic risk score including 175 variants, while near work and outdoor exposure in previous studies were used as dichotomous variables and individual SNPs or a GRS including 39 variants was used.[15, 17]

Parental myopia has been an established risk factor for years. Our study underscores the statistical evidence that parental myopia represents genetic as well environmental risk factors. According to the results of this and other studies, the predictive value for parental myopia (0.67) is as good as GRS (0.67) or ERS (0.69).[23, 43] To date, genetic testing for young children is not feasible in a clinical setting nor at population level, hence, determination of GRS is unlikely to become a routine procedure. Ascertainment of parental myopia and ERS is much easier to detect children at risk of myopia before the onset. Clinicians encountering myopic parents with young children should raise awareness about prevention of myopia by lifestyle.

In conclusion, our findings add to the evidence that increased near work and lack of outdoor exposure in childhood significantly enhance the effect of myopia genes. Changing children's lifestyle in this digital era requires action from all of those involved in child raising, starting with increasing awareness by knowledge dissemination.

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SUPPLEMENTS

Table S1. Variance AL/CR and myopia explained by Genetic risk scores

Genetic risk score	Meta- GWAS P-value threshold	N variants in score	Variance explained AL/CR (%)c N=3406	Variance explained myopia (%)d N=3291
Reference model[a]	NA	NA	1.9	2.4
Score 1[b]	5.00E-08	175	5.4	4.3
Score 2[b]	5.00E-07	248	5.3	4.3
Score 3[b]	5.00E-06	404	5.6	4.4
Score 4[b]	5.00E-05	784	5.4	4.4
Score 5[b]	5.00E-04	2,063	5.8	4.6
Score 6[b]	0.005	7,949	5.6	4.4
Score 7[b]	0.01	12,657	5.6	4.4
Score 8[b]	0.05	39,804	6.1	4.6
Score 9[b]	0.1	65,426	6.3	4.7
Score 10[b]	0.5	184,607	5.8	4.4
Score 11[b]	0.8	227,764	5.8	4.5
Score 12[b]	1	243,261	5.7	4.5

*a Reference model includes age, sex and first ten principal components. b Score 1-12: Reference model plus genetic risk scores for different P-value thresholds. c Explained variance is computed as: R^2 * 100%. d Explained variance is computed as: Nagelkerke R^2 * 100%. NA = not applicable.*

Table S2. Gene-Environment Correlations

N=3406	Effect of GRS on ERS[a]		
GRS thresholds	**Estimate**	**SE**	**P-value**
5.00E-08	0.031	0.022	0.16
5.00E-07	0.027	0.022	0.23
5.00E-06	0.035	0.020	0.09
5.00E-05	0.047	0.021	0.03
5.00E-04	0.058	0.021	<0.01
0.005	0.062	0.023	<0.01
0.01	0.053	0.023	0.02
0.05	0.056	0.021	<0.01
0.1	0.059	0.021	<0.01
0.5	0.055	0.023	0.02
0.8	0.056	0.023	0.01
1	0.056	0.023	0.01

a Environmental risk scores (ERS) and genetic risk scores (GRS) are standardized and adjusted for age, sex and first ten principal components. ERS = Environmental risk score; GRS = Genetic risk score; Estimate = Beta-coefficient; SE = standard error.

Table S3. Odds Ratios per risk score group for myopia

N=3291	OR[a]	95% CI	P-value	% myopes
Low GRS – low ERS	1.000	-	-	5.2
Low GRS –medium ERS	1.017	0.973-1.063	0.46	6.9
Low GRS – high ERS	1.061	1.012-1.111	0.01	12.2
Medium GRS – low ERS	0.999	0.955-1.045	0.95	5.7
Medium GRS – medium ERS	1.047	1.000-1.095	0.05	10.0
Medium GRS – high ERS	1.089	1.041-1.140	<0.01	14.5
High GRS – low ERS	1.044	0.997-1.093	0.07	9.7
High GRS – medium ERS	1.103	1.054-1.154	<0.01	15.3
High GRS – high ERS	1.232	1.177-1.288	<0.01	27.4

a Adjusted for age, sex and first ten principal components. The odds ratio for myopia versus no myopia for environmental risk score tertiles (low, medium or high) and genetic risk score tertiles (low, medium or high). The group with low environmental risk and low genetic risk served as the reference (i.e. OR = 1.0). OR = odds ratio, 95% CI = 95% Confidence Interval

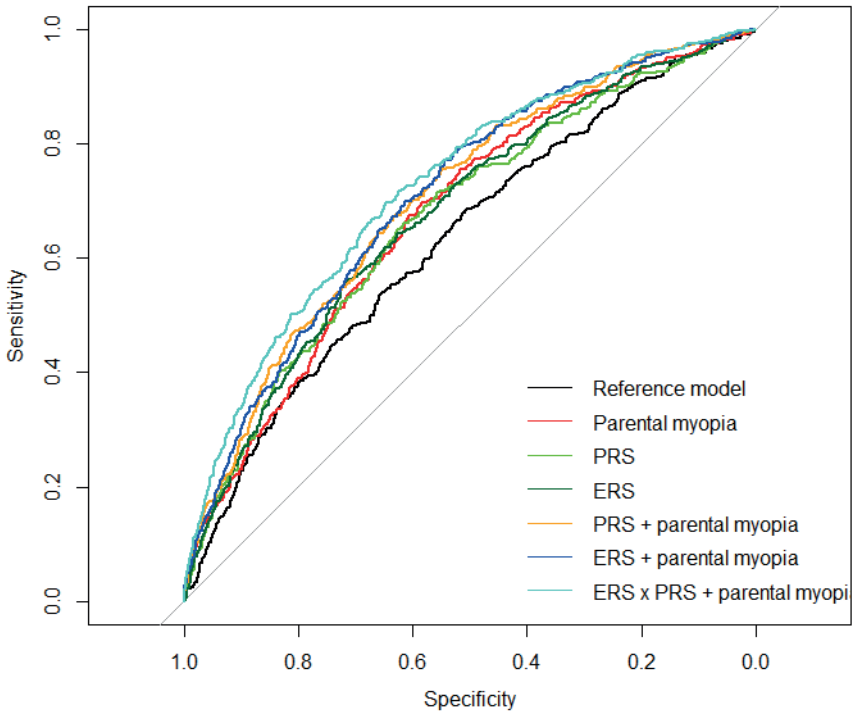

Figure S1. Receiver operating characteristic curve (ROC) of myopia versus no myopia
Graph showing the receiver operating characteristic (ROC) curve for myopia versus no myopia. Reference model includes age, sex and first ten principal components. All other models include the reference model. Parental myopia = Model including parental myopia; GRS = Model including genetic risk score; ERS = Model including environmental risk score; ERS + parental myopia = Model including environmental risk score and parental myopia; GRS + parental myopia = Model including genetic risk score and parental myopia; ERS x GRS + parental myopia = Model including environmental risk score, genetic risk score, the interaction term of environmental risk score and genetic risk score and parental myopia.

10

Evidence that emmetropization buffers against both genetic and environmental risk factors for myopia

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ABSTRACT

Purpose: To test the hypothesis that emmetropization buffers against genetic and environmental risk factors for myopia by investigating whether risk factor effect sizes vary depending on children's position in the refractive error distribution.

Methods: Refractive error was assessed in participants from 2 birth cohorts, Avon Longitudinal Study of Parents and Children (ALSPAC) (noncycloplegic autorefraction) and Generation R (cycloplegic autorefraction). A genetic risk score for myopia was calculated from genotypes at 146 loci. Time spent reading, time outdoors, and parental myopia were ascertained from parent-completed questionnaires. Risk factors were coded as binary variables (0=low, 1=high risk). Associations between refractive error and each risk factor were estimated using either ordinary least squares (OLS) regression or quantile regression.

Results: Quantile regression: effects associated with all risk factors (genetic risk; parental myopia; high time spent reading; low time outdoors) were larger for children in the extremes of the refractive error distribution than for emmetropes and low ametropes in the center of the distribution. For example, the effect associated with having a myopic parent for children in quantile 0.05 vs. 0.50 was: ALSPAC age 15, -1.19 D (95% CI -1.75 to -0.63) vs. -0.13 D (-0.19 to -0.06), p = 0.001; Generation R age 9, -1.31 D (-1.80 to -0.82) vs. -0.19 D (-0.26 to -0.11), p < 0.001. Effect sizes for OLS regression were intermediate to those for quantiles 0.05 and 0.50.

Conclusions: Risk factors for myopia were associated with much larger effects in children in the extremes of the refractive error distribution, providing indirect evidence that emmetropization buffers against both genetic and environmental risk factors.

INTRODUCTION

Myopia is a common eye disorder most often caused by axial elongation of the eye in childhood and adolescence. The prevalence of myopia is rising dramatically; 50% of young adults in Europe and 80% in urban areas in China are currently estimated to be myopic.[1, 2] Myopia is associated with retinal complications in adulthood, such as myopic macular degeneration, retinal detachment and glaucoma.[3-5] It is currently a leading cause of irreversible visual impairment and blindness.[5, 6]

Experimental models suggest that the development of myopia is a consequence of the emmetropization process influenced by a combination of genetic and environmental factors.[7] Genome-wide association studies have identified more than 150 genetic variants associated with refractive error.[8] Together these genetic variants explain ~8% of the phenotypic variance in adults and ~2% in children.[8, 9] Near work and lack of outdoor exposure are important environmental risk factors associated with myopia.[10, 11] Recent meta-analyses reported a 85% increased odds of myopia in children who performed a 'high' vs. 'low' level of near work and a 2% increased odds for every one diopter-hour of more near work per week, whereas 4.5 to 7.5 additional hours of outdoor exposure was associated with a 43% reduction in the risk of incident myopia.[10, 11] Parental myopia is another important risk factor and is often used as a proxy for genetic predisposition, but may also involve shared environmental effects.[9, 12] Many studies have reported an association between gender and myopia,[13, 14] usually with myopia being more common in girls than boys. This association may be caused in part by the association between puberty and myopia,[15] coupled with the earlier age of onset of puberty in girls.

Myopia and refractive error have been extensively investigated using conventional ordinary least square (OLS) linear and logistic regression in order to quantify the effects of genetic and environmental risk factors. In OLS analyses, it is assumed that the 'effect size' of each risk factor is consistent across the whole study population.[16] However, studies on other continuous phenotypes such as body mass index (BMI), height and birth weight have demonstrated that the effect of genetic and environmental factors can differ for individuals depending on where they lie in the phenotypic distribution.[17-20] For example, Williams (2012) reported that a polygenic risk score quantifying a person's genetic predisposition to a high or low BMI was associated with a 4.2-fold larger effect size in obese compared to very lean individuals.[19] In contrast to OLS regression, conditional quantile regression (CQR) can be used to determine the effect associated with a risk factor in specific quantiles of the phenotypic distribution.[16] In the current study, we applied CQR to test the hypothesis that genetic and environmental risk

factors for myopia exert larger effects in some children than others. Specifically, we explored whether the magnitude (in diopters) of risk factor-refractive error associations was larger in children who already had relatively high levels of ametropia.

METHODS

The Avon Longitudinal Study of Parents and Children (ALSPAC)

Pregnant women resident in Avon, England were recruited between April 1991 and December 1992. Of the initial pregnancies, there were 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. Accordingly, the total sample size increased to 15,454 pregnancies. Of these 14,901 were alive at 1 year of age. Information on the cohort parents and their offspring was collected using a variety of methodologies including self-completion questionnaires sent to study mothers, fathers, teachers and the study child, direct examination at the research clinic using standardized protocols, and linkage to educational data from the school system.[21, 22] The ALSPAC study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool: http://www.bristol.ac.uk/alspac/researchers/our-data/

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee (ALEC; IRB00003312; registered as 'U Bristol IRB #1' on the Office of Human Research Protections database) and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALEC at the time. Detailed information describing how the confidentiality of the cohort is maintained can be found at: http://www.bristol.ac.uk/alspac/researchers/research-ethics/

The Generation R Study

In this population-based prospective cohort study based in Rotterdam, The Netherlands, pregnant women were recruited between April 2002 and January 2006.[23, 24] Of the 9778 mothers enrolled in the study, 9749 gave birth to live born children. The exact methodology of the Generation R study has been described elsewhere.[23, 24] In short, information on the cohort parents and their offspring was collected by direct examination at the research clinic using standardized protocols, Magnetic Resonance Imaging (MRI), urine and blood samples, interviews and questionnaires. Children were invited to the research center at the age of 9 years, and 5862 (60%) of them participated. The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam (MEC 217.595/2002/20), and

conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants. More information in the study cohort measurements and collaborations can be found at: https://generationr.nl/researchers/.

Refractive error

ALSPAC participants were invited to attend a research clinic approximately once per year from the age of 7. For the research clinic visits scheduled when the children were aged 7, 10, 11, 12 and 15 years, noncycloplegic autorefraction was performed using a Canon R50 instrument (Canon USA Inc., Lake Success, NY). Generation R participants were invited to a research center at the age 9 years. The institutional review board approved the installation of cycloplegic eye drops midway through these research clinic visits; hence, a proportion of the 9-year-old participants received automated cycloplegic refractive error using a Topcon KR8900 instrument (Topcon, Tokyo, Japan). Specifically, 2395 (41.8%) of the 5862 Generation R attendees received cycloplegia, which consisted of 2 drops (three in case of dark irises) of 1% cyclopentolate instilled at 5-minute intervals at least 30 minutes before autorefraction. Pupil diameter was ≥ 6 mm at the time of measurement. Spherical equivalent was calculated as the sum of the full spherical value and half of the cylindrical value.

Questionnaire-derived risk factors

ALSPAC. When study participants were approximately 8 years of age, their mother or guardian was asked to complete a questionnaire item, "On a weekend day, how much time on average does your child spend each day out of doors in summer?", children were classified as spending a "high" amount of time outdoors if the response was "3 or more hours" and as "low" if the response was "1–2 hours", "less than 1 hours" or "not at all".[25] In answer to another question on the same questionnaire, "On normal days in school holidays, how much time on average does your child spend each day reading books for pleasure?", children were classified as spending a "high" amount of time reading if the response was "1–2 hours" or "3 or more hours" and as "low" if the response was "less than 1 hours" or "not at all".[25] Parental myopia was inferred from a questionnaire item completed by each parent separately during the time the study child's mother was pregnant, which asked, "How would you rate your sight without glasses?" as described previously.[12] Briefly, parents who responded for both eyes as "I can't see clearly at a distance" or "I can't see much at all" or a combination of these two responses were classed as being myopic. Parents who responded for both eyes as "always very good" or "I can't see clearly close up" or a combination of these two responses were classed as being non-myopic. Any other combination of responses resulted in the classification being set as "missing".

Generation R. When study participants were approximately 9 years-old, their mother or guardian was asked to complete the questionnaire items, "How many days per week does your child play outside" and "How long does your child approximately play outside per day".[26] Mean

weekly outdoor play was calculated by multiplying the amount of days × time. Walking or cycling to and from school was processed similarly. Total outdoor exposure was calculated as the sum of playing outside and walking or cycling to and from school. Children were classified as spending a "high" amount of time outdoors if the total weekly outdoor exposure was more than 7 hours and as "low" if the total weekly outdoor exposure was less than 7 hours. In answer to another question on the same questionnaire, "Does your child read in his or her spare time?", children were classified as spending a "high" amount of time reading if the response was "5 to 10 hours per week", "11 to 15 hours per week" or "over 15 hours per week" and as "low" if their answer was "never" or "less than 5 hours per week".[26] Parental myopia was inferred from the same questionnaire with the items, "Does the mother/father have glasses or contact lenses for either near (minus lenses) or far sightedness (plus lenses)?". Parental myopia was classified as 'one' when at least one of the parents was myopic and 'zero' otherwise.

Polygenic risk scores

Genotype data were available for 7,981 ALSPAC participants and 5,731 Generation R participants, after excluding individuals who withdrew consent (for details of genotyping and imputation see Taylor et al.[27] and Kruithof et al.[24]). Polygenic risk scores were calculated as the weighted number of risk alleles carried for 146 of 149 genetic variants associated with refractive error identified in a GWAS study by the CREAM consortium and 23andMe[8] (note that 3 of the 149 variants were excluded due to a low minor allele frequency[28]). Weightings were obtained as the regression coefficient for association with refractive error in diopters in the UK Biobank replication sample, as reported by Tedja et al.[8] Polygenic risk scores were standardized (to have a mean of zero) and then converted to a binary variable, which was coded as '1' if the polygenic risk score was less than zero and coded as '0' otherwise (such that 'genetic risk = 1' indicated an increased risk of a more negative refractive error).

Statistical analysis

The refractive error of each child was calculated as the average mean spherical equivalent in the two eyes. For ALSPAC, analyses were restricted to unrelated children of European genetic ancestry[12] who had valid autorefraction information from at least one research clinic visit and whose genotype data passed quality control checks.[27] For Generation R, analyses were restricted to children with valid cycloplegic refractive error measurement and whose genotype data passed quality control checks.[29] Because of the smaller sample size, all available Generation R participants were included irrespective of ethnicity or relatedness. Conditional quantile regression models[30] were fitted with the *quantreg* package in R, with refractive error as the dependent variable and risk factor exposure as an independent variable. Children were stratified into 19 quantiles, ranging from 0.05 (towards myopia) to 0.95 (towards hyperopia). Four established risk factors for myopia were evaluated - high genetic predisposition; parental

myopia; high time spent reading, and low time outdoors - with each coded as a binary variable (0 or 1), with 1 indicating a higher risk of myopia. As a control, we evaluated gender as a fifth potential risk factor. In previous work, gender was found to display negligible association with refractive error in the ALSPAC and Generation R samples[9, 25] and hence it was of interest to test whether a similar lack of association was observed in quantile regression analyses. The effect associated with each risk factor was evaluated using two approaches. First, 'conventional' univariate OLS linear regression analysis (which assumes the effect of the risk factor is the same in everybody) and second, univariate quantile regression analysis (which allows the effect of the risk factor to vary depending on where in the refractive error distribution an individual lies). For ALSPAC, separate models were fit for refractive error at age 7, 10, 12 or 15 years. As ALSPAC and Generation R are birth cohort studies, the age range of participants was narrow. Accordingly, the inclusion of a covariate indicating each child's precise age had minimal effect on parameter estimates, hence an age term was not included. A categorical covariate for self-reported ethnicity was included in the Generation R analyses (self-reported ethnicity was preferred to genetically assessed ethnicity because of a lower level of missing data). Self-reported ethnicity was the only covariate included in the Generation R analyses. No covariates were included in the ALSPAC analyses. The relationship between risk factor effect size and refractive error quantile was modeled using a Loess function with the *ggplot2* package.[31] Comparisons between the risk factor effect size at a specific quantile versus the risk factor effect size at quantile 0.50 (approximate emmetropia) was assessed by permutation, as described in Appendix 1 in the Supplementary Information. Also, for each risk factor, a test for a linear trend of increasing or decreasing effect size with age in ALSPAC participants was carried out using a random effects meta-regression model with the *metafor* package.[32] These trend tests were carried out separately for the effect sizes obtained by OLS regression and by CQR at each quantile. As sensitivity analyses, the primary analyses were repeated after imputing missing data using Multiple Imputation by Chained Equations (MICE), as described in Appendix 2 in the Supplementary Information.

RESULTS

Cohort demographics

The age and refractive error of children in the study sample are summarized in Table 1, stratified by research clinic target age. In the ALSPAC sample, after excluding participants with no genetic data, those of non-European genetic ancestry, and those related to other children in the sample, there were 6440 children with refractive error information available from at least one visit (5564, 5291, 4839 and 3687 children had information from the age 7, age 10, age 12 and age 15 research clinics, respectively). Of the full sample, 49.6% were female and 58.9% had one or two parents with myopia, while 41.8%, 20.3% and 19.5%, were missing information

regarding parental myopia, time spent reading and time spent outdoors, respectively. In the Generation R sample, 2395 participants attended the age 9 research clinic, underwent cycloplegic autorefraction, and had information regarding their ethnicity. Of this sample, 49.9% were female, 67.8% were of European ethnicity and 53% had one or two parents with myopia, while 40.0%, 35.8%, 34.4% and 18.0% were missing information regarding genotypes, parental myopia, time spent reading and time spent outdoors, respectively (Table 1).

Association between risk factor exposure and refractive error

Figure 1 illustrates how refractive error was distributed across quantiles of the trait in ALSPAC participants attending the age 15 research clinic and Generation R participants attending the age 9 research clinic. In the ALSPAC sample, conventional OLS regression analysis provided evidence that 4 of the 5 risk factors were associated with a more negative refractive error: a high genetic risk, having a parent with myopia, a high amount of time spent reading, and a low amount of time spent outdoors (Table 2). Gender showed little evidence of an association with refractive error in this sample, although there was weak evidence of an association at age 12 (beta = -0.07 D, 95% CI -0.14 to -0.00 D, $p = 0.040$ for females). The effect associated with the other 4 risk factors steadily increased in magnitude as children got older (e.g. the effect size was -0.06, -0.10, -0.15, and -0.21 D at the age 7, 10, 12 and 15 research clinics, respectively, in participants who spent a high vs. low time reading). In the Generation R sample, conventional OLS regression analysis provided evidence that 2 of the 5 risk factors were associated with a more negative refractive error: a high genetic risk (beta = -0.43 D, 95% CI -0.56 to -0.30, $p < 0.001$) and having a parent with myopia (beta = -0.35 D, 95% CI -0.47 to -0.22, $p < 0.001$) (Table 2). The effect associated with each risk factor in ALSPAC individuals attending the a15 research clinic, and Generation R individuals attending the age 9 research clinic is shown in Figure 2 (as a dashed line, with 95% confidence interval depicted with grey shading).

Table 1. Demographics characteristics of children with information available at each research clinic visit.

Research clinic	N	Gender [a] (Boys/ Girls)	Age [b] (Years)	Ethnicity (EUR/ non-EUR)	Refractive error [b] (D)	Genetic risk [a] Low/High/ Missing N (%)	Parental myopia [a] No/Yes/ Missing N (%)	Time reading [a] Low/High/ Missing N (%)	Time outdoors [a] Low/High/ Missing N (%)
ALSPAC									
Age 7	5564	2827/ 2737	7.53 (6.92 to 8.13)	5564/0	0.20 (-1.53 to 1.92)	2772/2792/0 (49.8/50.2/0.0)	1341/1979/2244 (24.1/35.6/40.3)	2923/1700/941 (52.5/30.6/16.9)	2210/2450/904 (39.7/44.0/16.2)
Age 10	5291	2622/ 2669	10.64 (10.15 to 11.13)	5291/0	0.06 (-2.06 to 2.19)	2645/2646/0 (50.0/50.0/0.0)	1269/1898/2124 (24.0/35.9/40.1)	2801/1679/811 (52.9/31.7/15.3)	2142/2376/773 (40.5/44.9/14.6)
Age 12	4839	2360/ 2479	12.81 (12.36 to 13.25)	4839/0	-0.16 (-2.45 to 2.12)	2423/2416/0 (50.1/49.9/0.0)	1154/1747/1938 (23.8/36.1/40.0)	2554/1544/741 (52.8/31.9/15.3)	1937/2195/707 (40.0/45.4/14.6)
Age 15	3687	1745/ 1942	15.43 (14.89 to 15.97)	3687/0	-0.38 (-2.89 to 2.12)	1850/1837/0 (50.2/49.8/0.0)	886/1387/1414 (24.0/37.6/38.4)	1958/1251/478 (53.1/33.9/13.0)	1449/1779/459 (39.3/48.3/12.4)
Generation R									
Age 9	2395	1200/ 1195	9.83 (9.82 to 9.85)	1625/770	0.75 (0.70 to 0.80)	718/720/957 (30.0/30.0/40.0)	718/820/857 (30.0/34.2/35.8)	973/599/823 (40.6/25.0/34.4)	995/968/432 (41.5/40.4/18.0)

[a] *Sample size in each category.*

[b] *Mean (95% confidence interval).*

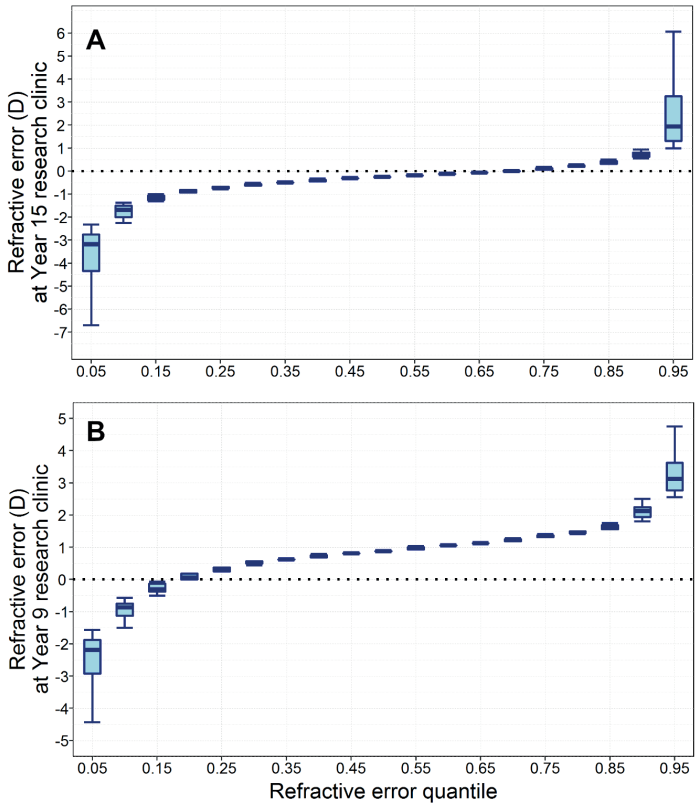

Figure 1. Distribution of refractive error by quantiles. Panel A, refractive error at the age 15 research clinic in ALSPAC participants. Panel B, refractive error at the age 9 research clinic in Generation R participants. Participants in each study sample were ranked by refractive error (most myopic to most hyperopic) and then divided into 19 equally sized bins (quantiles).

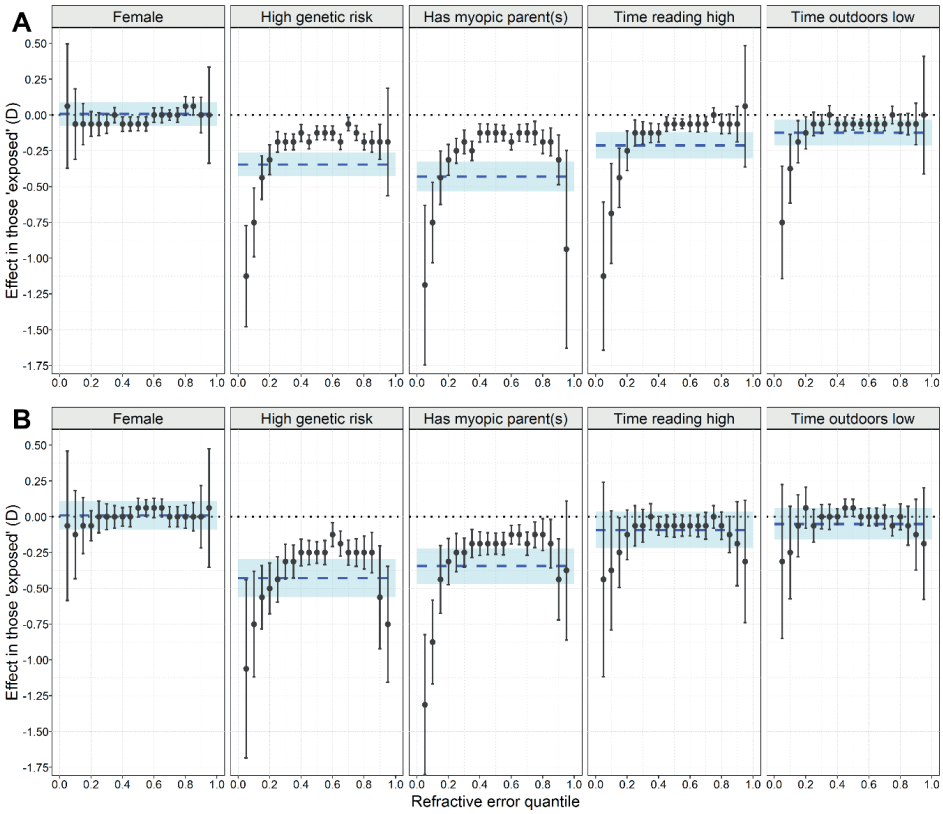

Figure 2. Comparison of effect sizes associated with risk factor exposure estimated with ordinary least squares (OLS) linear regression or with quantile regression. Panel A, refractive error at the age 15 research clinic in ALSPAC participants. Panel B, refractive error at the age 9 research clinic in Generation R participants. The dashed line indicates the effect size associated with exposure to the risk factor, calculated with OLS linear regression (95% confidence interval shown as grey shaded region). Filled circles correspond to the effect size associated with each exposure, calculated with quantile regression (error bars indicate 95% confidence interval). Note that effect sizes can vary across quantiles of the refractive error distribution for quantile regression.

Table 2. Effect sizes quantifying associations between risk factors and refractive error, evaluated using ordinary least squares (OLS) linear regression or quantile regression. All risk factors were coded as binary variables (0=lower risk and 1=higher risk category for myopia). Results for quantile regression are only presented for quantiles 0.05 and 0.50. The sample size at each age varies due to missing information for some risk factors.

				Ordinary Least Squares regression		Quantile regression: quantile 0.05		Quantile regression: quantile 0.50	
Risk factor	**Cohort**	**Research clinic**	**N**	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	**P-value**	**Beta (95% CI)**	***P*-value**
Female gender	ALSPAC	Age 7	5564	-0.016 (-0.062 to 0.030)	4.92E-01	0.000 (-0.090 to 0.090)	1.00E+00	0.000 (-0.030 to 0.030)	1.00E+00
		Age 10	5291	0.009 (-0.050 to 0.067)	7.66E-01	0.062 (-0.118 to 0.243)	4.98E-01	0.000 (-0.039 to 0.039)	1.00E+00
		Age 12	4839	-0.069 (-0.135 to -0.003)	3.98E-02	-0.188 (-0.448 to 0.073)	1.59E-01	0.000 (-0.031 to 0.031)	1.00E+00
		Age 15	3687	0.008 (-0.075 to 0.090)	8.54E-01	0.062 (-0.371 to 0.496)	7.78E-01	-0.062 (-0.111 to -0.014)	1.11E-02
	Generation R	Age 9	2395	0.010 (-0.091 to 0.111)	8.47E-01	-0.063 (-0.585 to 0.460)	8.15E-01	0.063 (-0.003 to 0.128)	6.21E-02
High genetic risk	ALSPAC	Age 7	5564	-0.163 (-0.209 to -0.117)	3.91E-12	-0.188 (-0.282 to -0.093)	1.00E-04	-0.125 (-0.155 to -0.095)	4.44E-16
		Age 10	5291	-0.235 (-0.293 to -0.177)	2.28E-15	-0.438 (-0.634 to -0.241)	1.30E-05	-0.125 (-0.155 to -0.095)	6.66E-16
		Age 12	4839	-0.300 (-0.365 to -0.235)	2.73E-19	-0.812 (-1.084 to -0.541)	4.54E-09	-0.125 (-0.156 to -0.094)	1.78E-15
		Age 15	3687	-0.345 (-0.427 to -0.264)	1.53E-16	-1.125 (-1.479 to -0.771)	5.01E-10	-0.125 (-0.173 to -0.077)	3.73E-07
	Generation R	Age 9	1437	-0.428 (-0.561 to -0.295)	4.01E-10	-1.063 (-1.685 to -0.440)	8.43E-04	-0.250 (-0.325 to -0.175)	9.68E-11

Table 2. Continued.

Risk factor	Cohort	Research clinic	N	Ordinary Least Squares regression		Quantile regression: quantile 0.05		Quantile regression: quantile 0.50	
				Beta (95% CI)	*P*-value	Beta (95% CI)	P-value	Beta (95% CI)	*P*-value
Has myopic parent(s)	ALSPAC	Age 7	3320	-0.257 (-0.313 to -0.202)	2.07E-19	-0.250 (-0.364 to -0.136)	1.81E-05	-0.125 (-0.158 to -0.092)	2.22E-13
		Age 10	3167	-0.350 (-0.423 to -0.278)	4.20E-21	-0.688 (-0.886 to -0.489)	1.45E-11	-0.125 (-0.169 to -0.081)	3.70E-08
		Age 12	2901	-0.388 (-0.470 to -0.306)	4.05E-20	-1.000 (-1.385 to -0.615)	3.80E-07	-0.125 (-0.167 to -0.083)	4.84E-09
		Age 15	2273	-0.430 (-0.533 to -0.327)	4.38E-16	-1.188 (-1.745 to -0.630)	3.10E-05	-0.125 (-0.186 to -0.064)	6.18E-05
	Generation R	Age 9	1537	-0.345 (-0.468 to -0.221)	5.69E-08	-1.313 (-1.801 to -0.824)	1.60E-07	-0.188 (-0.262 to -0.113)	1.02E-06
Time spent reading high	ALSPAC	Age 7	4623	-0.062 (-0.114 to -0.011)	1.77E-02	-0.188 (-0.327 to -0.048)	8.57E-03	0.000 (-0.032 to 0.032)	1.00E+00
		Age 10	4480	-0.104 (-0.170 to -0.038)	2.09E-03	-0.438 (-0.672 to -0.203)	2.52E-04	0.000 (-0.039 to 0.039)	1.00E+00
		Age 12	4098	-0.153 (-0.227 to -0.079)	4.86E-05	-0.750 (-1.111 to -0.389)	4.75E-05	-0.062 (-0.106 to -0.019)	4.77E-03
		Age 15	3209	-0.211 (-0.303 to -0.119)	7.04E-06	-1.125 (-1.642 to -0.608)	2.03E-05	-0.062 (-0.104 to -0.021)	2.86E-03
	Generation R	Age 9	1572	-0.092 (-0.220 to 0.035)	1.56E-01	-0.438 (-1.117 to 0.242)	2.07E-01	-0.063 (-0.142 to 0.017)	1.26E-01

Table 2. Continued.

Risk factor	Cohort	Research clinic	N	Ordinary Least Squares regression		Quantile regression: quantile 0.05		Quantile regression: quantile 0.50	
				Beta (95% CI)	*P*-value	Beta (95% CI)	P-value	Beta (95% CI)	*P*-value
Time spent outdoors low	ALSPAC	Age 7	4660	-0.051 (-0.100 to -0.001)	4.60E-02	-0.062 (-0.140 to 0.015)	1.15E-01	0.000 (-0.031 to 0.031)	1.00E+00
		Age 10	4518	-0.097 (-0.161 to -0.033)	3.01E-03	-0.312 (-0.514 to -0.111)	2.34E-03	0.000 (-0.040 to 0.040)	1.00E+00
		Age 12	4132	-0.122 (-0.194 to -0.051)	8.06E-04	-0.562 (-0.849 to -0.276)	1.19E-04	0.000 (-0.040 to 0.040)	1.00E+00
		Age 15	3228	-0.123 (-0.213 to -0.034)	7.15E-03	-0.750 (-1.143 to -0.357)	1.85E-04	-0.062 (-0.105 to -0.020)	4.28E-03
	Generation R	Age 9	1963	-0.051 (-0.160 to 0.058)	3.63E-01	-0.313 (-0.850 to 0.225)	2.54E-01	0.063 (0.003 to 0.122)	4.06E-02

Quantile regression analysis also suggested that the same 4 risk factors in the ALSPAC sample and the same 2 risk factors in the Generation R sample identified by OLS regression were associated with refractive error (Table 2; Supplementary Tables S1 and S2). In addition, this method yielded compelling evidence that the effect associated with exposure to each of these risk factors varied markedly between individuals (Figure 2; Supplementary Tables S1 and S2). The pattern of results was similar for the genetic risk score and for having a myopic parent. Namely, the effect size was of the order of -0.13 D for participants who were in the middle of the trait distribution, i.e. emmetropes and low ametropes, while the estimated effect size was increasingly larger for children in the more extreme quantiles. For example, the increased risk associated with having at least one myopic parent was seven to nine times larger for children in quantile 0.05 vs. quantile 0.50 in ALSPAC children aged 15 years (-1.19 D, 95% CI -1.75 to -0.63 D vs. -0.13 D, 95% CI -0.19 to -0.06 D, $p = 0.001$) as well as in Generation R children aged 9 years (-1.31 D, 95% CI -1.80 to -0.82 D vs. -0.19 D, 95% CI -0.26 to -0.11 D, $p < 0.001$) (Table 2; Supplementary Table S1). For time spent outdoors and time spent reading in the ALSPAC sample, the effect associated with the risk factor was very close to zero for children in quantiles 0.50 (approximate emmetropia) to 0.95 (hyperopia), while the effect size estimates became increasingly more negative for progressively lower quantiles (myopia). For the lowest quantile (0.05) the estimated effect size associated with a 'high' time reading was -1.13 D and the effect size associated with a 'low' time outdoors was -0.75 D ($p < 0.001$ and $p = 0.001$, respectively, for the comparison between quantile 0.05 vs. 0.50; Supplementary Table S1). There was minimal evidence of an association between refractive error and either time spent outdoors or time spent reading in the Generation R sample at any quantile, mirroring the OLS analysis results. Sensitivity analyses carried out after imputing missing data yielded similar effect size estimates to the original analyses, but with more precise confidence intervals (Supplementary Table S3 and Figure S1). This led to stronger support for an association of time spent reading and refractive error in the Generation R sample after imputation of missing data ($p = 0.031$ in OLS analysis and $p = 0.001$ for CQR at quantile 0.05; Supplementary Table S3).

Finally, quantile regression analysis was used to track the change in effect size associated with each risk factor across childhood in the ALSPAC sample (Figure 3A). There was evidence that children in the high genetic risk group and children with at least one myopic parent already had a more negative refractive error at age 7 years-old. This was true even for individuals in the middle of the trait distribution (e.g. at quantile 0.50, genetic risk beta = -0.13 D, $p < 0.001$ and parental myopia beta = -0.13 D, $p < 0.001$). This was not the case for time spent reading and time outdoors at age 7 years (at quantile 0.50, time reading beta = 0.00 D, $p = 1.00$ and parental myopia beta = 0.00 D, $p = 1.00$). For all risk factors except gender, effect sizes steadily increased with age (Figure 3A; Table 2). Tests for a linear trend of increasing effect size with age revealed statistical evidence supporting such increases for all risk factors except gender across quantiles

0.05 to 0.20 (Supplementary Table S4). However, there was no evidence to suggest that effect sizes increased linearly with age for children in the middle-and-higher quantiles (quantiles 0.50 to 0.95). The pattern of results in Generation R at age 9 (Figure 3B; Table 2) was broadly similar to that of ALSPAC children at age 10. Sensitivity analyses after imputing missing data yielded similar results (Supplementary Figure S2).

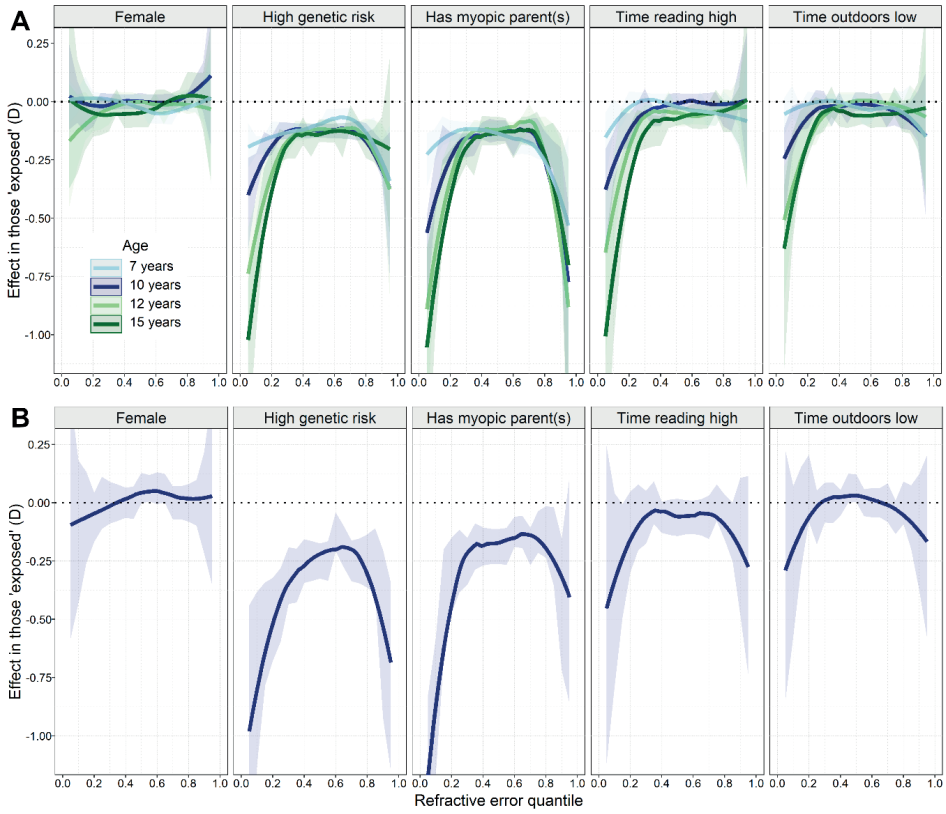

Figure 3. Pattern of effect sizes associated with risk factor exposure estimated with quantile regression. Panel A, refractive error at the age 7 to age 15 research clinics in ALSPAC participants. Panel B, refractive error at the age 9 research clinic in Generation R participants. The fitted lines indicate the effect size associated with exposure to the risk factor (shaded regions indicate 95% confidence interval of Loess fit).

DISCUSSION

In the ALSPAC and Generation R birth cohorts we observed evidence that both genetic and environmental risk factors were associated with large, inter-individual variations in effect on refractive error. In other words, the effect of being exposed to one of the risk factors was not the same for all children. This inter-individual variation was not apparent when conventional OLS linear regression was used. In the main analyses, parental myopia and the genetic risk score were associated with refractive error in both ALSPAC and Generation R. However, reading time and time outdoors were associated with refractive error in ALSPAC, but not in the Generation R cohort. The absence of an association in Generation R for the two environmental risk factors may be due to limited power, since the beta-coefficients for near work and outdoor exposure in Generation R were very similar to the ALSPAC age 7 cohort but the sample size was smaller, leading to lower precision. In support of this theory, analysis of the Generation R sample using multiple imputation of missing data *did* provide evidence of an association with near work (OLS analysis, beta = -0.29 D, 95% CI -0.53 to -0.04, p = 0.031; CQR analysis for quantile 0.05, beta = -0.86 D, 95% CI -1.41 to -0.32, p = 0.001). Moreover, these environmental risk factors have previously been associated with myopia and axial elongation in a larger sample from Generation R when the exposures were modelled as continuous variables.[9, 33] Our results highlighted differences in effect size profiles for genetic and environmental factors. Most evidently, genetic risk and parental myopia were associated with refractive error in children from both the myopic and the hyperopic arms of the refractive error distribution, whereas environmental factors were only associated with refractive error in children in the myopic arm of the distribution, tentatively suggesting that myopia may be both genetically and environmentally driven, while hyperopia may be only genetically driven. In contrast, gender showed little variation in effects across different quantiles and the CQR effect size estimate was comparable to that obtained by OLS linear regression. It was not possible to determine whether effect sizes were larger for genetic than for environmental risk factors, because the risk factors would have been measured with varying degrees of imprecision and error (for example, a parental questionnaire is known to be a crude method of quantifying time spent outdoors[34]).

Further analysis stratifying children by age suggested that effects on refractive error associated with the risk exposures were not fixed. Instead, there was evidence for a monotonic increase in genetic and environmental effect size estimates with additional years of age, restricted to quantiles 0.05 to 0.30. The difference between the youngest (7 years) and the oldest (15 years) ALSPAC participants was most pronounced for children in quantile 0.05 (i.e. those with the most myopic refractive error) and reached as much as 0.93 D. Our OLS analyses also showed an increased effect with age for all risk factors except gender (Supplementary Table S4) although the evidence was weaker for time spent outdoors (p = 0.07) than for the other risk factors (all $p \leq 0.002$). Age-dependent effects have been established in previous studies regarding

genetics, for example it has been reported that specific genetic variants may have 'early' or 'late' effects.[35, 36] Regarding environmental effects, a meta-analysis of outdoor exposure stratified by age showed conflicting results, while the effect of near work stratified by age has not been studied in detail.[10, 11]

To our knowledge, this is the first study investigating environmental risk factors for myopia using quantile regression. As regards genetic risk, a recent quantile regression study proposed visually-guided emmetropization to be the mechanism by which effect size heterogeneity arises.[28] Emmetropization is a process that is influenced by both genetic and environmental (visual) factors.[37] Mutti et al. have proposed that emmetropizatory lens thinning has a limit to the amount of axial elongation that it can compensate for.[38] Given the age range of our study population, we extend this hypothesis and suggest that emmetropization might have a protective effect not only against myopia- or hyperopia-predisposing genetic risk factors, but also myopia-inducing environmental risk factors such as time spent reading or time spent outdoors. Together with our finding that the effects of genetic and environmental risk factors increase with age, we hypothesize that for those individuals whose emmetropization compensation limit is surpassed, genetic and environmental risk factors could lead to greater effects.

Gene-environment interactions have been identified in adult and child population using genetic risk scores and education or an environmental sum score.[9, 39] Analyses of the adult and child populations from the Consortium for Refractive Error and Myopia (CREAM) resulted in only a few gene-environment interactions using individual genetic variants and education or near work.[36, 40, 41] In the absence of interactions (such as gene-environment interactions) all individuals would be expected to respond to risk factors in the same way. However, our analysis identified a high degree of variability from person to person, hinting towards potential involvement of gene-environment or other kinds of interaction (i.e. gene-gene or environment-environment interactions). For example, an individual's genetic risk remains essentially fixed during the lifetime and yet we see effect size heterogeneity not only for one age category (for example, age 15), but across different age groups. Therefore, we suggest that genetic effects on refractive error may depend on the amount of time an individual has been exposed to an environmental risk factor. Therefore, lifestyle changes may be particularly beneficial for children destined to reach the extreme myopic arm of the refractive error distribution by adulthood (although identifying such children prior to myopia development is challenging).[42, 43] Myopia control interventions, such as atropine eye drops or orthokeratology, may be particularly beneficial in these children.[44, 45] With reference to the various treatment interventions for myopia, it has been reported that certain children respond particularly well to a specific intervention while others respond poorly.[44] This is reminiscent of the inter-individual variation in risk factor effect sizes revealed here by quantile regression

analysis. Thus, we propose that quantile regression analysis of clinical trial data may be an informative future direction for research aimed at better understanding the causes of inter-individual treatment responses.

A strength of this study is the triangulation of research methods. Both OLS and CQR analyses were performed in two cohorts to minimize bias and to strengthen our conclusions. Furthermore, in the ALSPAC cohort, noncycloplegic refractive error measurements were performed up to five times from age 7 to age 15 which allowed us to analyze patterns over childhood. Because of the large sample size of the ALSPAC cohort, we had the opportunity to exclude children of non-European ethnicity and familially related children to ensure that these factors did not influence our findings. The use of cycloplegia in the Generation R cohort made this cohort ideal as a replication sample to investigate the impact of the absence of cycloplegia in ALSPAC. Unfortunately, the smaller sample size of Generation R necessitated that children of non-European ethnicity and related children were *not* excluded. We were limited by the use of questionnaire data for near work, outdoor exposure and parental myopia which may have influenced our results because of coarse-grained response options, and errors in gauging the duration of children's past behavior by parents. Furthermore, the criteria used to define time spent outdoors and time spent reading as being either 'high' or 'low' differed between ALSPAC and Generation R. It was not possible to standardize classification criteria across the two studies since ALSPAC and Generation R utilized different questions and response options to gauge time outdoors and time reading. The classification criteria we adopted were, in general, those employed in previous investigations of risk factors for myopia.[25, 26, 36] The exception to this was time outdoors in the Generation R study, which was previously modelled as a continuous variable, but here was dichotomized to split the sample into two groups of approximately equal size.[26, 33] Analyses of the two cohorts also differed regarding the ethnicity of the participants: all ALSPAC participants were of European ancestry, while approximately 32% of Generation R participants were of non-European ancestry. The inclusion of children with diverse ethnic backgrounds may have increased effect size estimates in the Generation R cohort relative to ALSPAC if, as has previously been suggested, myopia risk factor effect sizes are larger in children of non-European ethnicity.[40]

We were also limited by the high level of missing data for both cohorts, especially for the risk factors derived from questionnaire responses (time spent outdoors, time spent reading, and parental myopia). Sensitivity analyses carried out after imputing missing data provided comparable results to the original analyses, suggesting that the high level of missing data would have had little impact so long as these data were missing at random. Should the data not have been missing at random, this could have biased both the OLS and CQR effect size estimates. A third limitation was that refractive error in the ALSPAC cohort was assessed without cycloplegia. A comparison of noncycloplegic autorefraction and cycloplegic retinoscopy

in ALSPAC children who had pinhole visual acuity >0.2 logMAR at age 7 (n=414) revealed an average discrepancy of -0.13 D (standard deviation 0.53 D).[46] At age 15, a comparison of noncycloplegic autorefraction and optometrist spectacle prescriptions in ALSPAC participants (n=346 individuals with data available from the age 15 clinic visit and an optometrist spectacle prescription within ±6 months) yielded an average error of -0.22 D (standard deviation 0.84 D).[47] At both ages the negative bias in estimates of refractive error due to lack of cycloplegia was greater in those with hyperopia than those with myopia, as reported previously.[48] Therefore, this source of measurement error could have affected the estimation of risk factor effect sizes at certain quantiles more than at other quantiles. Specifically, if the higher quantiles (comprising children in the hyperopic arm of the refractive error distribution) were relatively more affected by measurement error then this may have led to the attenuation of risk factor effect size estimates for these higher quantiles. This phenomenon would in turn have attenuated the difference in effect size between high vs. middle quantiles, e.g. quantiles 0.95 vs. 0.50 (although we caution that the effects of measurement error can be difficult to predict).[49] Notably, the inverted U-shape of the risk factor effect size vs. quantile relationship was apparent for both the ALSPAC and Generation R cohorts, which provided reassurance that measurement error resulting from lack of cycloplegia was not a major contributor to the this inverted U-shaped relationship. Cycloplegic refractive error measurements were introduced 1.5 years after the start of the Generation R age 9 research clinic. We restricted our analysis to the 2395 children who received cycloplegia. We expect this selection process of excluding children who did not undergo cycloplegic autorefraction not to have introduced bias, but rather to have reduced the statistical power of the analyses. Finally, we chose to examine binary risk factors in order to simplify interpretation, but this may also have led to reduced statistical power in our models.

In conclusion, quantile regression analysis of two large, population-based birth cohorts provided evidence that both genetic and environmental risk factors for myopia have widely differing impacts in different individuals (e.g. seven-fold or more). Our findings are consistent with the idea that each person's final position in the refractive error distribution is the result not only of their level of genetic risk and their exposure to environmental risk factors, but also their emmetropization system's ability to buffer against these risk factors.

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SUPPLEMENTS

Appendix 1. Testing for a difference in risk factor effect size at a specific quantile vs. the risk factor effect size at quantile 0.5

The following steps were performed in R to test for a difference in risk factor effect size at a specific quantile vs. the risk factor effect size at quantile 0.5. The analysis assumes that the ratio of those exposed vs. non-exposed to the risk factor of interest is approximately 1:1.

1. Load sample dataset containing information on refractive error (coded as a continuous variable) and the risk factor of interest (coded, 1=exposed, 0=non-exposed) for N participants.
2. Run a quantile regression analysis at quantiles 0.05, 0.10, 0.15, ..., 0.95 with refractive error as the dependent variable and risk factor exposure as the predictor variable.
3. Name the resulting effect size estimate at each quantile as Eff_q for q=0.05, 0.10, 0.15, ..., 0.95 and the corresponding standard errors as SE_q.
4. Store the results.
5. Randomly assign each participant as being exposed or non-exposed to a simulated risk factor, i.e. create a random binomial variable (0,1).
6. Create a simulated refractive error phenotype by adding the observed median effect for the risk factor of interest ($Eff_{0.50}$) to the observed refractive error of the participant.
7. Run a quantile regression analysis at quantiles 0.05, 0.10, 0.15, ..., 0.95 with the simulated refractive error as the dependent variable and the simulated risk factor exposure as the predictor variable.
8. Name the resulting effect size estimate at each quantile as $SimEff_q$ for q=0.05, 0.10, 0.15, ..., 0.95 and the corresponding standard errors and variances as $SimSE_q$ and $SimVar_q$.
9. Calculate a Z-score for the difference between median and each quantile:

$$Z = \frac{SimEff_{0.50} - SimEff_q}{\sqrt{\frac{SimVar_{0.50}}{N} + \frac{SimVar_q}{N}}}$$

10. Store the resulting Z-scores.
11. Repeat steps [5-10] 10,000 times.
12. Calculate how often the observed Z-scores from step [4] would occur in the simulated data from step [11].

R code for conducting the above analyses

```
library(quantreg)
mydata  <- [read in data file]
names(mydata) <- c("obsMSE","obsExposed")
n  <- dim(mydata)[1]
nperm  <- 10000

get_zscore  <- function(x1,x2,sd1,sd2,n){
a  <- as.numeric(x1) - as.numeric(x2)
b  <- ((as.numeric(sd1)^2)/as.numeric(n)) +
 ((as.numeric(sd2)^2)/as.numeric(n))
c  <- a/(b^0.5)
return(c)
}

# Quantile regression analysis for observed risk factor
# ------------------------------------------------------
results  <- as.data.frame(matrix(ncol=19,nrow=6))
row.names(results) <- c("beta","se","p","sd","Z","empircal_pval_vs_median")

# Quantile regression analysis for observed risk factor: median effect
mod_qr  <- rq(formula=obsMSE ~ obsExposed, data=mydata, tau=0.5)
mod_sum  <- summary(mod_qr)
results[1,10]  <- mod_sum$coefficients[2,1]
results[2,10]  <- mod_sum$coefficients[2,2]
results[3,10]  <- mod_sum$coefficients[2,4]
results[4,10]  <- mod_sum$coefficients[2,2] * (n^0.5)
x2  <- mod_sum$coefficients[2,1]
sd2  <- mod_sum$coefficients[2,2] * (n^0.5)

# Quantile regression analysis for observed risk factor: effect at other quantiles
for (i in 1:19){
names(results)[i]  <- paste("Q",5*i,sep="")
q <- i/20
mod_qr  <- rq(formula=obsMSE ~ obsExposed, data=mydata, tau=q)
mod_sum  <- summary(mod_qr)
results[1,i]  <- mod_sum$coefficients[2,1]
results[2,i]  <- mod_sum$coefficients[2,2]
results[3,i]  <- mod_sum$coefficients[2,4]
results[4,i]  <- mod_sum$coefficients[2,2] * (n^0.5)
x1  <- mod_sum$coefficients[2,1]
```

```
sd1   <- mod_sum$coefficients[2,2] * (n^0.5)
if(i!=10){ results[5,i] <- abs(get_zscore(x1,x2,sd1,sd2,n)) }
}
results

# Quantile regression analysis for simulated risk factor
# ------------------------------------------------------
presults   <- as.data.frame(matrix(nrow=nperm,ncol=19))
median_effect  <- as.numeric(results[1,10])
for (p in 1:nperm){
mygroup   <- rbinom(n,size=1,prob=0.5)
myphen  <- mydata$obsMSE + (mygroup*median_effect)
mod_qrmed  <- rq(formula=myphen ~ mygroup, tau=0.5)
mod_summed  <- summary(mod_qrmed)
x2 <- mod_summed$coefficients[2,1]
sd2   <- mod_summed$coefficients[2,2]* (n^0.5)
for (i in 1:19){
q <- i/20
mod_qr  <- rq(formula=myphen ~ mygroup, tau=q)
mod_sum   <- summary(mod_qr)
x1 <- mod_sum$coefficients[2,1]
sd1   <- mod_sum$coefficients[2,2]* (n^0.5)
if(i!=10){ presults[p,i] <- abs(get_zscore(x1,x2,sd1,sd2,n)) }c
}
}

# Calculate empirical p-values
for (i in 1:19){
if(i!=10){
 obs   <- results[5,i]
 y <- presults[,i]
 e <- ecdf(y)
 results[6,i]  <- 1 - e(obs)
 }
}
results
```

Appendix 2. Imputation of missing data for sensitivity analysis.

Missing data were imputed using Multiple Imputation by Chained Equations (MICE)[1,2] under the assumption that data were missing at random. The following variables were used for ALSPAC: Birth weight; month of birth, maternal age, maternal social class, paternal social class, gender, time outdoors, time reading, number of myopic parents, genetic risk score, number of clinic visits attended, age at Year 7 clinic visit, age at Year 10 clinic visit, age at Year 11 clinic visit, age at Year 12 clinic visit, age at Year 15 clinic visit, refractive error at Year 7 clinic visit, refractive error at Year 10 clinic visit, refractive error at Year 11 clinic visit, refractive error at Year 12 clinic visit, refractive error at Year 15 clinic visit. Similar variables were used for Generation R, only maternal and paternal social class was replaced by maternal and paternal education and net household income. Imputation was performed with the *mice* package in R, with settings of 5 imputed datasets and a maximum of 50 iterations.

The OLS linear regression and quantile regression analysis steps were repeated for the imputed data. Parameters estimates, standard errors and p-values for the quantile regression analysis pooled across imputed datasets were done under the simplifying assumption of multivariate normality.

Table S1. Risk factor effect size estimates for ALSPAC participants at the Year 15 research clinic. Beta coefficients correspond to the estimated effect in diopters associated with high-risk vs. low-risk status.

Risk factor	High genetic risk score			At least 1 parent with myopia			Low time spent outdoors			High time spent reading		
	Beta (95% C.I.)	*P*-value[1]	*P*-value[2]	Beta (95% C.I.)	*P*-value[1]	*P*-value[2]	Beta (95% C.I.)	*P*-value[1]	*P*-value[2]	Beta (95% C.I.)	*P*-value[1]	*P*-value[2]
Quantile												
0.05	-1.125 (-1.479 to -0.771)	5.01E-10	<0.001	-1.188 (-1.745 to -0.630)	3.10E-05	0.001	-0.750 (-1.143 to -0.357)	1.85E-04	0.001	-1.125 (-1.642 to -0.608)	2.03E-05	<0.001
0.10	-0.750 (-0.990 to -0.510)	9.49E-10	<0.001	-0.750 (-1.031 to -0.469)	1.92E-07	<0.001	-0.375 (-0.614 to -0.136)	2.14E-03	0.010	-0.688 (-1.036 to -0.339)	1.14E-04	0.001
0.15	-0.438 (-0.590 to -0.285)	1.83E-08	<0.001	-0.438 (-0.624 to -0.251)	4.42E-06	<0.001	-0.188 (-0.335 to -0.040)	1.29E-02	0.090	-0.438 (-0.644 to -0.231)	3.42E-05	<0.001
0.20	-0.313 (-0.416 to -0.209)	3.61E-09	0.002	-0.313 (-0.420 to -0.205)	1.20E-08	0.001	-0.125 (-0.237 to -0.013)	2.88E-02	0.511	-0.25 (-0.388 to -0.112)	3.72E-04	0.002
0.25	-0.188 (-0.258 to -0.117)	2.34E-07	0.329	-0.250 (-0.337 to -0.163)	2.00E-08	0.006	-0.063 (-0.145 to 0.020)	1.37E-01	0.393	-0.125 (-0.216 to -0.034)	7.23E-03	0.374
0.30	-0.188 (-0.243 to -0.132)	5.75E-11	0.175	-0.188 (-0.270 to -0.105)	9.69E-06	0.205	-0.063 (-0.129 to 0.004)	6.67E-02	0.385	-0.125 (-0.203 to -0.047)	1.76E-03	0.339
0.35	-0.188 (-0.243 to -0.132)	4.07E-11	0.370	-0.250 (-0.317 to -0.183)	2.89E-13	0.001	0.000 (-0.065 to 0.065)	1.00E+00	0.308	-0.125 (-0.192 to -0.058)	2.60E-04	0.298
0.40	-0.125 (-0.184 to -0.066)	3.49E-05	0.476	-0.125 (-0.189 to -0.061)	1.21E-04	0.113	-0.063 (-0.107 to -0.018)	6.11E-03	0.391	-0.125 (-0.189 to -0.061)	1.28E-04	0.304
0.45	-0.188 (-0.236 to -0.139)	5.20E-14	0.139	-0.125 (-0.187 to -0.063)	7.37E-05	0.058	-0.063 (-0.112 to -0.013)	1.43E-02	0.452	-0.063 (-0.114 to -0.011)	1.64E-02	0.454
0.50	-0.125 (-0.173 to -0.077)	3.73E-07	NA	-0.125 (-0.186 to -0.064)	6.18E-05	NA	-0.063 (-0.105 to -0.020)	4.28E-03	NA	-0.063 (-0.104 to -0.021)	2.86E-03	NA
0.55	-0.125 (-0.174 to -0.076)	4.93E-07	0.355	-0.125 (-0.179 to -0.071)	6.11E-06	0.074	-0.063 (-0.096 to -0.029)	2.41E-04	0.511	-0.063 (-0.097 to -0.028)	3.21E-04	0.498
0.60	-0.125 (-0.175 to -0.075)	1.07E-06	0.420	-0.188 (-0.243 to -0.132)	5.28E-11	0.078	-0.063 (-0.114 to -0.011)	1.75E-02	0.538	-0.063 (-0.115 to -0.010)	2.00E-02	0.540
0.65	-0.188 (-0.240 to -0.135)	3.32E-12	0.159	-0.125 (-0.183 to -0.067)	2.88E-05	0.139	-0.063 (-0.108 to -0.017)	6.55E-03	0.324	-0.063 (-0.118 to -0.007)	2.65E-02	0.301

Table S1. Continued.

Risk factor	High genetic risk score			At least 1 parent with myopia			Low time spent outdoors			High time spent reading		
	Beta (95% C.I.)	*P*-value[1]	*P*-value[2]	Beta (95% C.I.)	*P*-value[1]	*P*-value[2]	Beta (95% C.I.)	*P*-value[1]	*P*-value[2]	Beta (95% C.I.)	*P*-value[1]	*P*-value[2]
0.70	-0.063 (-0.110 to -0.015)	1.01E-02	0.555	-0.125 (-0.187 to -0.063)	8.35E-05	0.168	-0.063 (-0.110 to -0.015)	1.06E-02	0.578	-0.063 (-0.114 to -0.011)	1.84E-02	0.574
0.75	-0.125 (-0.176 to -0.074)	1.69E-06	0.835	-0.125 (-0.206 to -0.044)	2.58E-03	0.233	0.000 (-0.062 to 0.062)	1.00E+00	0.797	0.000 (-0.051 to 0.051)	1.00E+00	0.097
0.80	-0.188 (-0.243 to -0.132)	4.51E-11	0.242	-0.188 (-0.269 to -0.106)	6.90E-06	0.194	-0.063 (-0.130 to 0.005)	6.85E-02	0.568	-0.063 (-0.131 to 0.006)	7.44E-02	0.545
0.85	-0.188 (-0.260 to -0.115)	3.56E-07	0.490	-0.188 (-0.285 to -0.090)	1.61E-04	0.224	-0.063 (-0.137 to 0.012)	9.82E-02	0.649	-0.063 (-0.129 to 0.004)	6.72E-02	0.626
0.90	-0.188 (-0.310 to -0.065)	2.70E-03	0.652	-0.313 (-0.486 to -0.139)	4.26E-04	0.015	-0.063 (-0.207 to 0.082)	3.96E-01	0.774	-0.063 (-0.188 to 0.063)	3.28E-01	0.730
0.95	-0.188 (-0.564 to 0.189)	3.29E-01	0.801	-0.938 (-1.628 to -0.247)	7.80E-03	0.003	0.000 (-0.410 to 0.410)	1.00E+00	0.720	0.063 (-0.361 to 0.486)	7.73E-01	0.537

[1] *P-value for test of null hypothesis that beta coefficient at that quantile equals zero.*

[2] *P-value for test of null hypothesis that the beta coefficient at that quantile is the same magnitude as the beta coefficient for quantile 0.50.*

Table S2. Risk factor effect size estimates for Generation R at the Year 9 research clinic. Beta coefficients correspond to the estimated effect in diopters for the high-risk vs. low-risk group.

	High genetic risk score			At least 1 parent with myopia			Low time spent outdoors			High time spent reading		
Risk factor	**Beta (95% C.I.)**	***P*-value[1]**	**P-value[2]**	**Beta (95% C.I.)**	***P*-value[1]**	***P*-value[2]**	**Beta (95% C.I.)**	***P*-value[1]**	***P*-value[2]**	**Beta (95% C.I.)**	***P*-value[1]**	**P-value[2]**
Quantile												
0.05	-1.063 (-1.685 to -0.440)	8.43E-04	0.007	-1.313 (-1.801 to -0.824)	1.60E-07	<0.001	-0.313 (-0.850 to 0.225)	2.54E-01	0.160	-0.438 (-1.117 to 0.242)	2.07E-01	0.358
0.10	-0.750 (-1.119 to -0.381)	7.10E-05	0.003	-0.875 (-1.168 to -0.582)	5.97E-09	<0.001	-0.250 (-0.573 to 0.073)	1.29E-01	0.041	-0.375 (-0.792 to 0.042)	7.79E-02	0.208
0.15	-0.563 (-0.784 to -0.341)	6.92E-07	0.002	-0.438 (-0.674 to -0.201)	3.05E-04	0.013	-0.063 (-0.279 to 0.154)	5.72E-01	0.211	-0.250 (-0.494 to -0.006)	4.47E-02	0.075
0.20	-0.50 (-0.678 to -0.322)	4.36E-08	0.002	-0.313 (-0.474 to -0.151)	1.56E-04	0.089	0.063 (-0.081 to 0.206)	3.93E-01	0.664	-0.125 (-0.298 to 0.048)	1.56E-01	0.454
0.25	-0.438 (-0.595 to -0.280)	6.09E-08	0.016	-0.250 (-0.384 to -0.116)	2.58E-04	0.537	-0.063 (-0.178 to 0.053)	2.88E-01	0.006	-0.063 (-0.203 to 0.078)	3.83E-01	0.650
0.30	-0.313 (-0.434 to -0.191)	5.08E-07	0.152	-0.250 (-0.350 to -0.150)	1.09E-06	0.132	0.000 (-0.085 to 0.085)	1.00E+00	0.016	-0.063 (-0.176 to 0.051)	2.82E-01	0.556
0.35	-0.313 (-0.428 to -0.197)	1.27E-07	0.338	-0.188 (-0.286 to -0.089)	2.09E-04	0.472	0.000 (-0.088 to 0.088)	1.00E+00	0.110	0.000 (-0.092 to 0.092)	1.00E+00	0.271
0.40	-0.250 (-0.343 to -0.157)	1.77E-07	0.754	-0.188 (-0.269 to -0.106)	7.79E-06	0.879	0.000 (-0.055 to 0.055)	1.00E+00	<0.001	-0.063 (-0.129 to 0.004)	6.67E-02	0.815
0.45	-0.250 (-0.335 to -0.165)	9.31E-09	0.294	-0.188 (-0.263 to -0.112)	1.32E-06	0.521	0.063 (0.000 to 0.125)	4.93E-02	0.200	-0.063 (-0.138 to 0.013)	1.06E-01	0.525
0.50	-0.250 (-0.325 to -0.175)	9.68E-11	NA	-0.188 (-0.262 to -0.113)	1.02E-06	NA	0.063 (0.003 to 0.122)	4.06E-02	NA	-0.063 (-0.142 to 0.017)	1.26E-01	NA
0.55	-0.250 (-0.335 to -0.165)	9.31E-09	0.413	-0.188 (-0.267 to -0.108)	4.04E-06	0.898	0.000 (-0.058 to 0.058)	1.00E+00	0.001	-0.063 (-0.136 to 0.011)	9.67E-02	0.698
0.60	-0.125 (-0.209 to -0.041)	3.49E-03	<0.001	-0.125 (-0.190 to -0.060)	1.57E-04	0.134	0.000 (-0.062 to 0.062)	1.00E+00	0.032	-0.063 (-0.134 to 0.009)	8.82E-02	0.776
0.65	-0.188 (-0.275 to -0.100)	3.04E-05	0.177	-0.125 (-0.195 to -0.055)	4.49E-04	0.008	0.000 (-0.063 to 0.063)	1.00E+00	0.041	-0.063 (-0.140 to 0.015)	1.16E-01	0.864

Table S2. Continued.

	High genetic risk score			At least 1 parent with myopia			Low time spent outdoors			High time spent reading		
Risk factor	**Beta (95% C.I.)**	***P*-value[1]**	**P-value[2]**	**Beta (95% C.I.)**	***P*-value[1]**	***P*-value[2]**	**Beta (95% C.I.)**	***P*-value[1]**	***P*-value[2]**	**Beta (95% C.I.)**	***P*-value[1]**	**P-value[2]**
0.70	-0.250 (-0.337 to -0.163)	2.44E-08	0.353	-0.188 (-0.268 to -0.107)	4.93E-06	0.411	0.000 (-0.083 to 0.083)	1.00E+00	0.213	-0.063 (-0.155 to 0.030)	1.88E-01	0.469
0.75	-0.250 (-0.346 to -0.154)	3.86E-07	0.667	-0.125 (-0.214 to -0.036)	6.11E-03	0.414	-0.063 (-0.134 to 0.009)	8.72E-02	0.003	0.000 (-0.078 to 0.078)	1.00E+00	0.398
0.80	-0.250 (-0.364 to -0.136)	1.87E-05	0.455	-0.125 (-0.236 to -0.014)	2.68E-02	0.453	0.000 (-0.091 to 0.091)	1.00E+00	0.174	-0.063 (-0.159 to 0.034)	2.06E-01	0.509
0.85	-0.250 (-0.390 to -0.110)	4.90E-04	0.733	-0.188 (-0.356 to -0.019)	2.94E-02	0.767	-0.063 (-0.199 to 0.074)	3.69E-01	0.076	-0.125 (-0.252 to 0.002)	5.32E-02	0.158
0.90	-0.563 (-0.922 to -0.203)	2.19E-03	0.074	-0.438 (-0.720 to -0.155)	2.45E-03	0.052	-0.125 (-0.372 to 0.122)	3.22E-01	0.110	-0.188 (-0.482 to 0.107)	2.12E-01	0.300
0.95	-0.750 (-1.155 to -0.345)	2.90E-04	0.008	-0.375 (-0.860 to 0.110)	1.30E-01	0.466	-0.188 (-0.578 to 0.203)	3.47E-01	0.141	-0.313 (-0.740 to 0.115)	1.52E-01	0.138

[1] *P-value for test of null hypothesis that beta coefficient at that quantile equals zero.*

[2] *P-value for test of null hypothesis that the beta coefficient at that quantile is the same magnitude as the beta coefficient for quantile 0.50.*

Table S3. Effect sizes quantifying associations between risk factors and refractive error, evaluated using ordinary least squares (OLS) linear regression or quantile regression after imputation of missing data using MICE.

				Ordinary Least Squares regression		Quantile regression: quantile 0.05		Quantile regression: quantile 0.50	
Risk factor	**Cohort**	**Research clinic**	**N**	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value**
Female gender	ALSPAC	Year 7	6504	-0.009 (-0.054 to 0.035)	6.83E-01	0.000 (-0.077 to 0.077)	1.00E+00	0.000 (-0.029 to 0.029)	1.00E+00
		Year 10	6504	0.001 (-0.054 to 0.056)	9.69E-01	0.012 (-0.168 to 0.193)	8.92E-01	0.000 (-0.037 to 0.037)	1.00E+00
		Year 12	6504	-0.046 (-0.107 to 0.015)	1.38E-01	-0.138 (-0.408 to 0.133)	3.20E-01	0.000 (-0.029 to 0.029)	1.00E+00
		Year 15	6504	-0.027 (-0.104 to 0.049)	4.92E-01	-0.050 (-0.400 to 0.300)	7.80E-01	-0.025 (-0.106 to 0.056)	5.68E-01
	Generation R	Year 9	2395	0.01 (-0.091 to 0.111)	8.47E-01	-0.062 (-0.585 to 0.46)	8.14E-01	0.062 (-0.003 to 0.128)	6.20E-02
High genetic risk	ALSPAC	Year 7	6504	-0.165 (-0.211 to -0.119)	9.30E-12	-0.188 (-0.266 to -0.109)	2.60E-06	-0.125 (-0.152 to -0.098)	<2.00E-16
		Year 10	6504	-0.242 (-0.298 to -0.185)	6.66E-16	-0.488 (-0.673 to -0.302)	4.34E-07	-0.138 (-0.204 to -0.071)	6.55E-03
		Year 12	6504	-0.290 (-0.351 to -0.228)	<2.00E-16	-0.875 (-1.129 to -0.621)	1.45E-10	-0.125 (-0.154 to -0.096)	<2.00E-16
		Year 15	6504	-0.344 (-0.413 to -0.275)	<2.00E-16	-1.075 (-1.362 to -0.788)	8.20E-12	-0.125 (-0.155 to -0.095)	2.22E-16
	Generation R	Year 9	2395	-0.278 (-0.389 to -0.166)	2.98E-06	-0.5 (-1.158 to 0.158)	1.53E-01	-0.138 (-0.226 to -0.049)	6.59E-03
Has myopic parent(s)	ALSPAC	Year 7	6504	-0.244 (-0.313 to -0.175)	2.00E-05	-0.212 (-0.353 to -0.072)	1.94E-02	-0.125 (-0.155 to -0.095)	<2.00E-16
		Year 10	6504	-0.335 (-0.404 to -0.266)	3.39E-10	-0.675 (-0.843 to -0.507)	1.10E-13	-0.112 (-0.229 to 0.004)	1.22E-01
		Year 12	6504	-0.398 (-0.488 to -0.308)	1.27E-06	-1.062 (-1.377 to -0.748)	2.42E-07	-0.125 (-0.155 to -0.095)	<2.00E-16

Table S3. Continued.

Risk factor	Cohort	Research clinic	N	Ordinary Least Squares regression		Quantile regression: quantile 0.05		Quantile regression: quantile 0.50	
				Beta (95% CI)	*P*-value	Beta (95% CI)	*P*-value	Beta (95% CI)	*P*-value
		Year 15	6504	-0.450 (-0.553 to -0.347)	5.17E-06	-1.325 (-1.641 to -1.009)	2.51E-10	-0.175 (-0.242 to -0.108)	1.99E-03
	Generation R	Year 9	2395	-0.326 (-0.446 to -0.207)	2.38E-06	-0.938 (-1.418 to -0.457)	1.60E-04	-0.175 (-0.257 to -0.093)	9.28E-04
Time spent reading high	ALSPAC	Year 7	6504	-0.055 (-0.103 to -0.007)	2.56E-02	-0.150 (-0.301 to 0.001)	8.03E-02	0.000 (-0.030 to 0.030)	1.00E+00
		Year 10	6504	-0.116 (-0.173 to -0.059)	6.71E-05	-0.462 (-0.711 to -0.214)	4.84E-04	0.000 (-0.032 to 0.032)	1.00E+00
		Year 12	6504	-0.167 (-0.236 to -0.098)	7.61E-06	-0.750 (-1.118 to -0.382)	3.05E-04	-0.038 (-0.117 to 0.042)	3.94E-01
		Year 15	6504	-0.203 (-0.272 to -0.134)	1.43E-08	-0.912 (-1.281 to -0.544)	1.64E-05	-0.062 (-0.099 to -0.026)	9.26E-04
	Generation R	Year 9	2395	-0.285 (-0.529 to -0.04)	3.07E-02	-0.862 (-1.407 to -0.318)	1.49E-03	-0.162 (-0.292 to -0.033)	1.83E-02
Time spent outdoors low	ALSPAC	Year 7	6504	-0.062 (-0.114 to -0.009)	2.54E-02	-0.112 (-0.202 to -0.023)	2.30E-02	0.000 (-0.029 to 0.029)	1.00E+00
		Year 10	6504	-0.093 (-0.158 to -0.027)	8.22E-03	-0.325 (-0.607 to -0.043)	4.57E-02	-0.012 (-0.079 to 0.054)	7.26E-01
		Year 12	6504	-0.130 (-0.198 to -0.062)	3.49E-04	-0.512 (-0.864 to -0.161)	1.03E-02	0.000 (-0.029 to 0.029)	1.00E+00
		Year 15	6504	-0.145 (-0.215 to -0.074)	9.83E-05	-0.750 (-1.065 to -0.435)	7.86E-06	-0.075 (-0.144 to -0.006)	7.08E-02
	Generation R	Year 9	2395	-0.055 (-0.168 to 0.057)	3.38E-01	-0.238 (-0.749 to 0.274)	3.63E-01	0.025 (-0.070 to 0.120)	6.17E-01

Table S4. Tests for a linear trend of increasing effect size with age. A negative beta coefficient indicates an increasingly negative (more myopic) effect size with age.

	Female gender		High genetic risk		Has myopic parent(s)		Time spent reading high		Time spent outdoors low	
Quantile	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value**
0.05	-0.007 (-0.048 to 0.034)	7.32e-01	-0.114 (-0.149 to -0.079)	1.95e-10	-0.136 (-0.183 to -0.088)	2.58e-08	-0.109 (-0.158 to -0.059)	1.59e-05	-0.09 (-0.126 to -0.054)	9.20e-07
0.10	-0.011 (-0.032 to 0.009)	2.81e-01	-0.069 (-0.096 to -0.041)	8.08e-07	-0.076 (-0.101 to -0.051)	1.61e-09	-0.073 (-0.101 to -0.045)	3.94e-07	-0.055 (-0.078 to -0.031)	4.31e-06
0.15	-0.020 (-0.039 to -0.001)	3.99e-02	-0.029 (-0.052 to -0.005)	1.59e-02	-0.041 (-0.063 to -0.019)	1.98e-04	-0.034 (-0.052 to -0.015)	4.32e-04	-0.018 (-0.037 to 0.001)	6.73e-02
0.20	-0.010 (-0.021 to 0.000)	5.15e-02	-0.024 (-0.035 to -0.013)	2.74e-05	-0.024 (-0.036 to -0.011)	2.09e-04	-0.031 (-0.045 to -0.017)	1.93e-05	-0.020 (-0.032 to -0.008)	7.43e-04
0.25	-0.009 (-0.019 to 0.001)	8.17e-02	-0.012 (-0.031 to 0.008)	2.37e-01	-0.015 (-0.026 to -0.005)	5.16e-03	-0.019 (-0.029 to -0.008)	6.23e-04	-0.012 (-0.031 to 0.007)	2.22e-01
0.30	-0.010 (-0.020 to 0.000)	4.74e-02	-0.010 (-0.019 to -0.001)	3.80e-02	-0.010 (-0.020 to 0.000)	4.32e-02	-0.014 (-0.023 to -0.005)	2.75e-03	-0.009 (-0.017 to -0.002)	1.81e-02
0.35	0.000 (-0.007 to 0.007)	1.00e+00	-0.005 (-0.013 to 0.002)	1.44e-01	-0.012 (-0.029 to 0.005)	1.68e-01	-0.015 (-0.023 to -0.006)	5.02e-04	-0.002 (-0.016 to 0.013)	8.42e-01
0.40	-0.006 (-0.013 to 0.001)	1.05e-01	0.000 (-0.007 to 0.007)	1.00e+00	0.000 (-0.008 to 0.008)	1.00e+00	-0.015 (-0.023 to -0.007)	2.62e-04	-0.007 (-0.014 to 0.001)	8.61e-02
0.45	-0.006 (-0.013 to 0.001)	1.01e-01	-0.006 (-0.013 to 0.002)	1.37e-01	0.000 (-0.008 to 0.008)	1.00e+00	-0.006 (-0.013 to 0.001)	1.01e-01	-0.005 (-0.019 to 0.008)	4.26e-01
0.50	-0.006 (-0.014 to 0.002)	1.48e-01	0.000 (-0.006 to 0.006)	1.00e+00	0.000 (-0.008 to 0.008)	1.00e+00	-0.009 (-0.016 to -0.002)	1.14e-02	-0.007 (-0.014 to 0.001)	8.46e-02
0.55	0.001 (-0.014 to 0.016)	9.25e-01	-0.008 (-0.017 to 0.000)	5.00e-02	0.000 (-0.007 to 0.007)	1.00e+00	-0.002 (-0.015 to 0.011)	7.89e-01	0.000 (-0.015 to 0.015)	9.77e-01
0.60	0.008 (0.000 to 0.017)	4.90e-02	-0.008 (-0.017 to 0.000)	4.91e-02	0.003 (-0.011 to 0.016)	7.13e-01	-0.001 (-0.015 to 0.012)	8.37e-01	0.001 (-0.014 to 0.016)	9.16e-01
0.65	0.005 (-0.008 to 0.019)	4.53e-01	-0.014 (-0.021 to -0.007)	5.43e-05	0.008 (-0.001 to 0.018)	7.97e-02	-0.01 (-0.019 to 0.000)	4.50e-02	-0.006 (-0.015 to 0.002)	1.20e-01

Table S4. Continued.

	Female gender		High genetic risk		Has myopic parent(s)		Time spent reading high		Time spent outdoors low	
Quantile	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value**
0.70	0.007 (0.000 to 0.015)	6.46e-02	-0.001 (-0.015 to 0.014)	9.46e-01	0.010 (-0.006 to 0.026)	2.23e-01	-0.002 (-0.016 to 0.012)	7.81e-01	0.002 (-0.011 to 0.015)	7.35e-01
0.75	0.000 (-0.007 to 0.007)	1.00e+00	0.000 (-0.007 to 0.007)	1.00e+00	0.009 (-0.002 to 0.020)	1.26e-01	0.005 (-0.008 to 0.019)	4.32e-01	0.002 (-0.012 to 0.016)	7.94e-01
0.80	0.006 (-0.003 to 0.015)	2.07e-01	-0.007 (-0.015 to 0.002)	1.21e-01	0.003 (-0.011 to 0.017)	6.60e-01	-0.005 (-0.019 to 0.009)	4.52e-01	-0.009 (-0.018 to 0.000)	5.33e-02
0.85	0.005 (-0.008 to 0.019)	4.55e-01	-0.005 (-0.019 to 0.010)	5.05e-01	0.009 (-0.006 to 0.025)	2.43e-01	0.002 (-0.013 to 0.017)	7.73e-01	-0.005 (-0.019 to 0.009)	4.66e-01
0.90	0.000 (-0.017 to 0.016)	9.85e-01	0.010 (-0.008 to 0.027)	2.84e-01	0.007 (-0.02 to 0.034)	6.14e-01	0.007 (-0.027 to 0.041)	6.80e-01	0.009 (-0.01 to 0.028)	3.59e-01
0.95	-0.003 (-0.049 to 0.043)	8.97e-01	0.014 (-0.041 to 0.069)	6.23e-01	-0.057 (-0.155 to 0.04)	2.50e-01	0.011 (-0.045 to 0.066)	7.03e-01	0.024 (-0.030 to 0.077)	3.88e-01
OLS	0.000 (-0.015 to 0.014)	9.53E-01	-0.024 (-0.035 to -0.013)	8.42E-06	-0.023 (-0.036 to -0.010)	5.35E-04	-0.018 (-0.030 to -0.006)	2.48E-03	-0.011 (-0.022 to 0.001)	6.81E-02

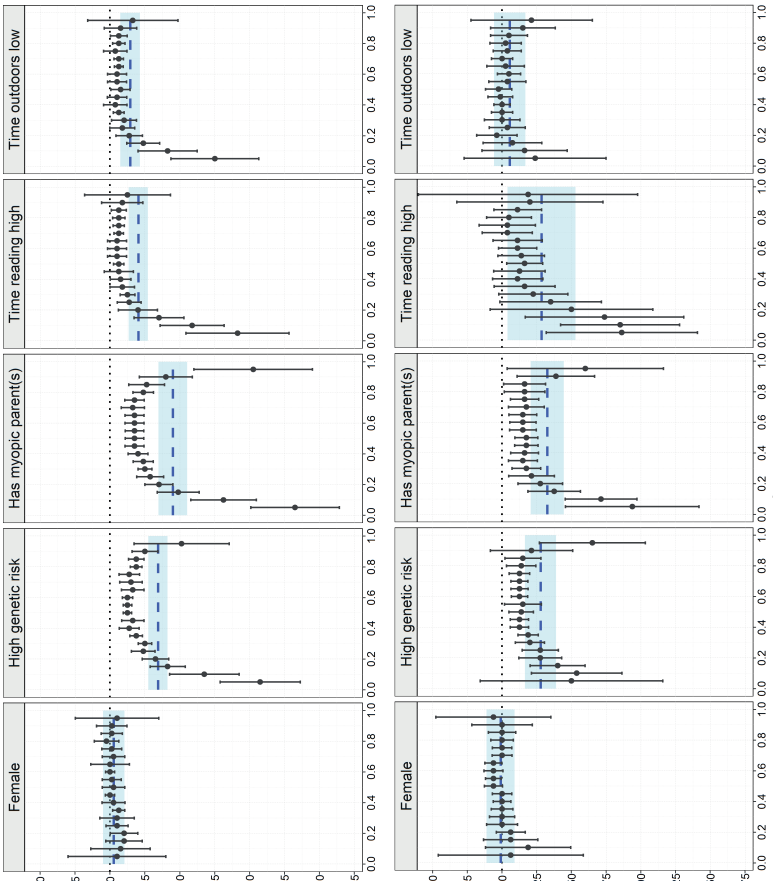

Figure S1. Comparison of effects associated with risk factor exposure estimated with ordinary least squares (OLS) linear regression or with quantile regression after imputing missing data via MICE. Panel A, refractive error at the Year 15 research clinic in ALSPAC participants. Panel B, refractive error at the Year 9 research clinic in Generation R participants. The dashed blue line indicates the effect associated with exposure to the risk factor, calculated with OLS linear regression (95% confidence interval shown as light blue shaded region). Filled circles correspond to the effect associated with each exposure, calculated with quantile regression (error bars indicate 95% confidence interval). Note that effect sizes can vary across quantiles of the refractive error distribution for quantile regression.

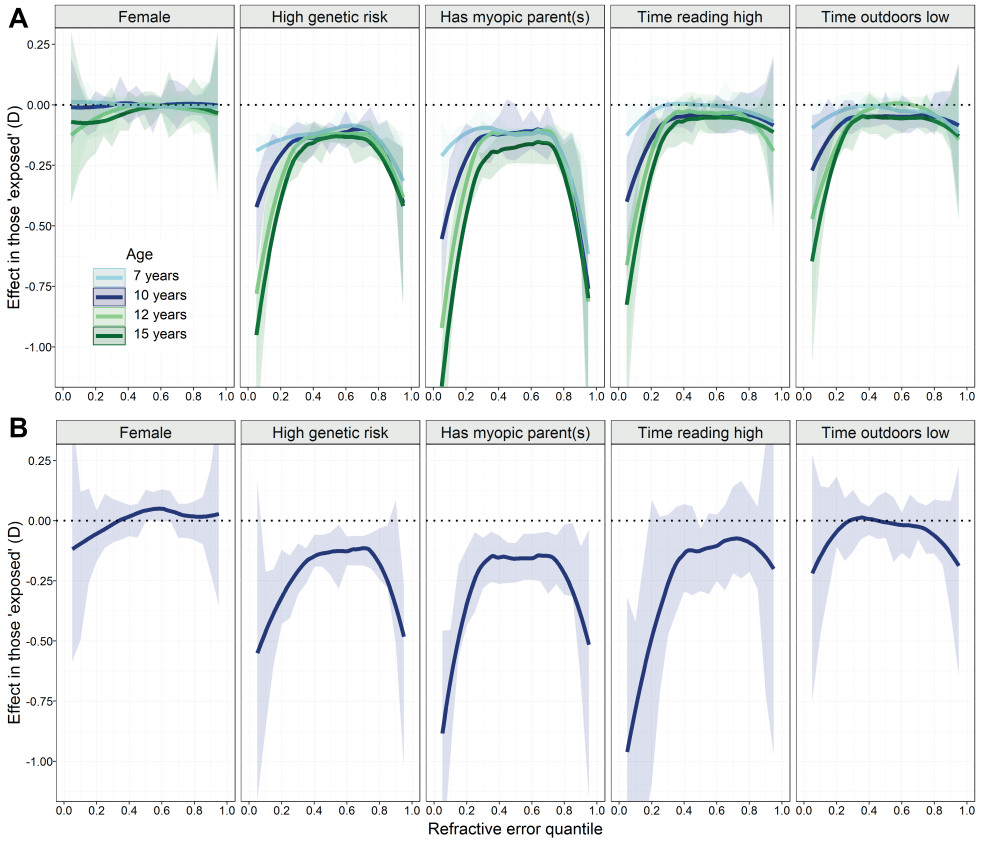

Figure S2. Effects associated with risk factor exposure estimated with quantile regression after imputing missing data via MICE. Panel A, refractive error at the Year 7 to Year 15 research clinics in ALSPAC participants. Panel B, refractive error at the Year 9 research clinic in Generation R participants. The fitted lines indicate the effect associated with exposure to the risk factor (shaded regions indicate 95% confidence interval of Loess fit).

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1. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Br Med J* 2009;339:b2393.
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Part VI

Maatschappelijke relevantie voor Nederland

10

11

12

Waarom dragen steeds meer kinderen een bril?

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Praktische Pediatrie
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SAMENVATTING

Myopie (bijziendheid) komt steeds vaker voor: bijna 50% van alle jongvolwassenen in Europa is momenteel myoop. Myopie – en vooral hoge myopie – is geassocieerd met slechtziendheid of zelfs blindheid op latere leeftijd. Myopie ontstaat door een combinatie van genetische en omgevingsfactoren. Inmiddels zijn er meer dan 500 genetische varianten voor deze oogafwijking geïdentificeerd. Het doen van veel 'dichtbijwerk' verhoogt het risico op myopie, terwijl veel buiten spelen het risico juist verlaagt. De door ons gelanceerde 20-20-2-regel is een praktisch advies om myopie te voorkomen: kijk na 20 minuten dichtbijwerk 20 seconden in de verte en ga 2 uur per dag naar buiten. Vooral kinderen tot en met 12 jaar met progressieve myopie komen in aanmerking voor behandeling en moeten worden verwezen naar een oogzorgteam gespecialiseerd in myopiecontrole. Wanneer de mate van myopie hoger is dan de leeftijd, moet aanvullend erfelijkheidsonderzoek worden overwogen.

INLEIDING

Lichtstralen die het oog binnenkomen, convergeren door het hoornvlies en de ooglens, waarna ze samenkomen in een brandpunt achter deze structuren. Bij een emmetroop (normaalziend) oog zonder refractieafwijking valt het brandpunt precies op het netvlies en ziet men zonder bril scherp. Bij een verziend oog valt het brandpunt achter het oog en is een pluslens nodig om het brandpunt naar het netvlies te verplaatsen; bij een myoop oog valt het brandpunt vóór het netvlies; een bril met minsterkte is dan nodig voor een brandpunt op het netvlies (figuur 1). Er is een sterke correlatie tussen de refractieafwijking en de aslengte van het oog. Myopie betekent dat het oog te lang is in verhouding tot de optische componenten in het oog. Het wordt gedefinieerd als een sterkte van minimaal –0,5 dioptrie of lager, hoge myopie als een sterkte van –6 dioptrie of lager. De prevalentie van myopie is de afgelopen jaren enorm gestegen. In Europa is de prevalentie toegenomen van 15,9% in de leeftijdsgroep 65-69 jaar tot 47,2% in de leeftijdsgroep 25-29 jaar.[1] De stedelijke gebieden in Oost-Azië lopen voorop in de cijfers: inmiddels is daar 80 tot 90% van de jongvolwassenen myoop.[2] Geschat wordt dat in 2050 de helft van de wereldbevolking myoop en ongeveer 10% hoog myoop zal zijn.[3] In dit artikel leggen wij uit waarom myopie een probleem is, wat de oorzaken van myopie zijn en wat u als zorgprofessional kunt doen.

Refractieafwijkingen

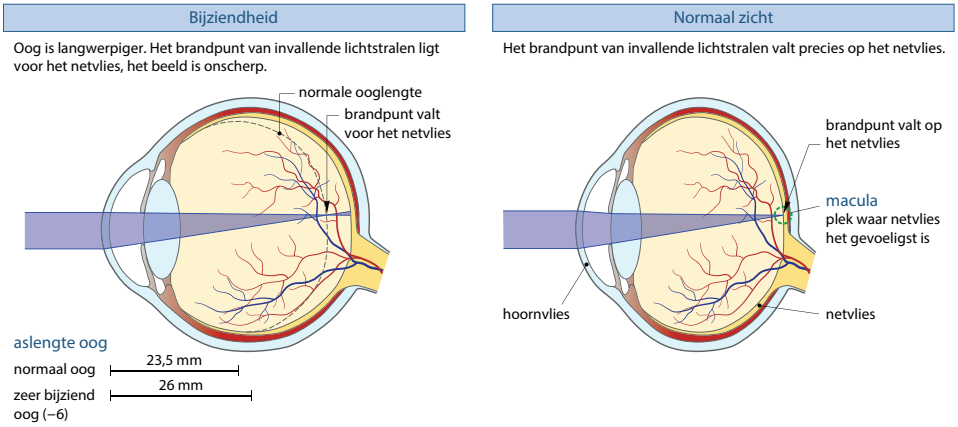
Er bestaan drie verschillende refractieafwijkingen.

- Myopie (bijziendheid): het brandpunt van invallende lichtstralen valt vóór het netvlies, een bril met minsterkte is nodig om scherp te zien (figuur 1).
- Hypermetropie (verziendheid): het brandpunt van invallende lichtstralen valt achter het netvlies, een bril met plussterkte is nodig om scherp te zien en/of hoofdpijn te voorkomen.
- Astigmatisme (cilinderafwijking): doordat het hoornvlies of de ooglens ovaal is in plaats van rond, komen invallende lichtstralen niet samen in één brandpunt, maar in een brandlijn. Een bril met cilindersterkte is nodig om scherp te zien.

EMMETROPISATIE EN MYOPIE

Vrijwel iedereen wordt met een klein oog geboren, met een gemiddelde aslengte van 16,5 mm.[4] Net zoals de rest van het lichaam groeit het oog nog tot op jongvolwassen leeftijd. Dit proces heet emmetropisatie; in de ideale situatie is het oog op jongvolwassen leeftijd gegroeid naar precies refractie nul dioptrie (emmetropie) met een gemiddelde aslengte van 23,5 mm. Dit wordt meestal op de leeftijd van 18 jaar bereikt. Wanneer een oog op de kinderleeftijd te hard groeit, wordt emmetropie al op jongere leeftijd bereikt. De groei gaat echter nog door waardoor

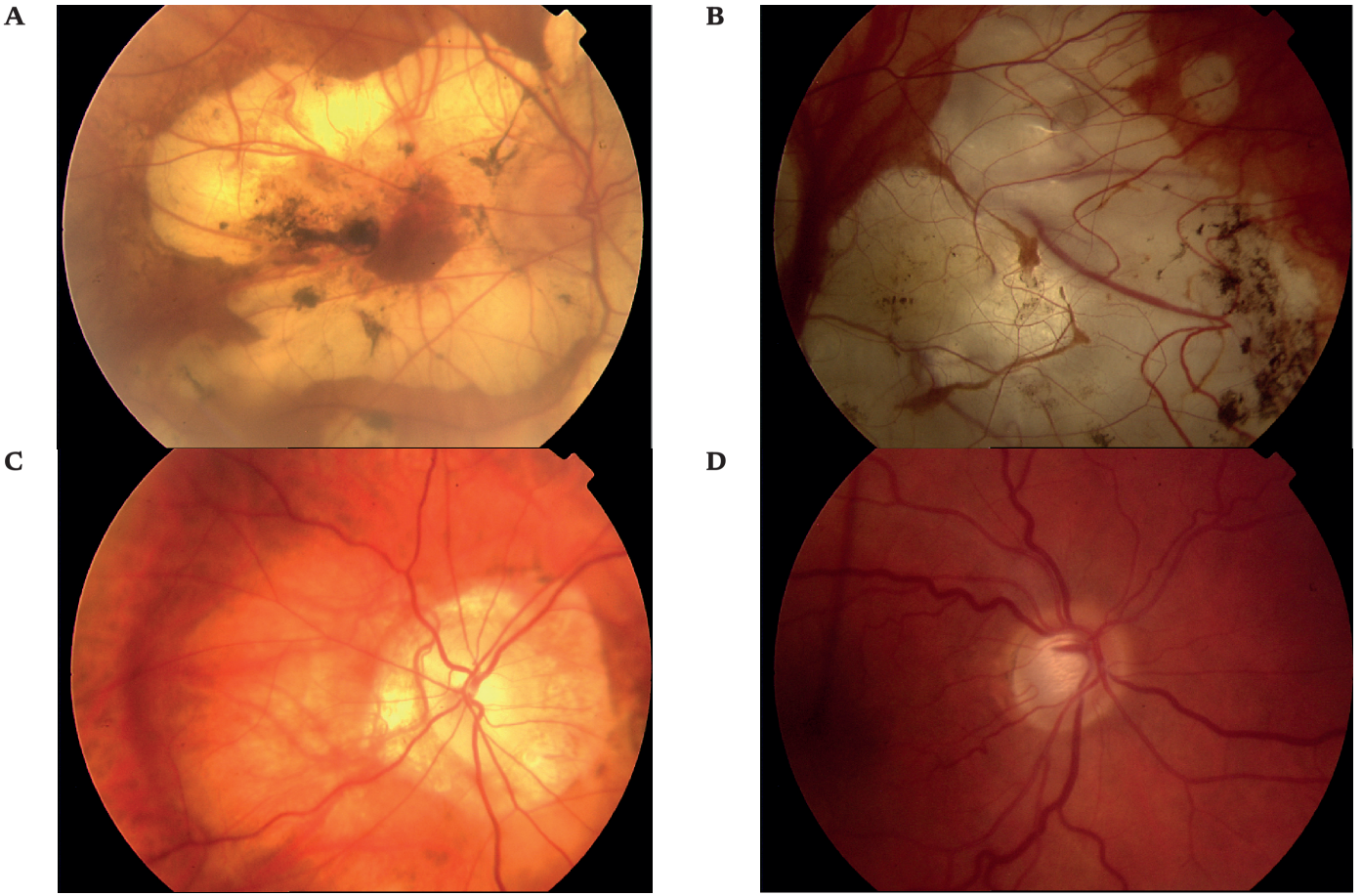
myopie ontstaat. Kinderen die op de basisschoolleeftijd al myopie ontwikkelen, hebben een grote kans om op volwassen leeftijd hoge myopie te ontwikkelen, met een bijbehorende aslengte van 26 mm.[5]



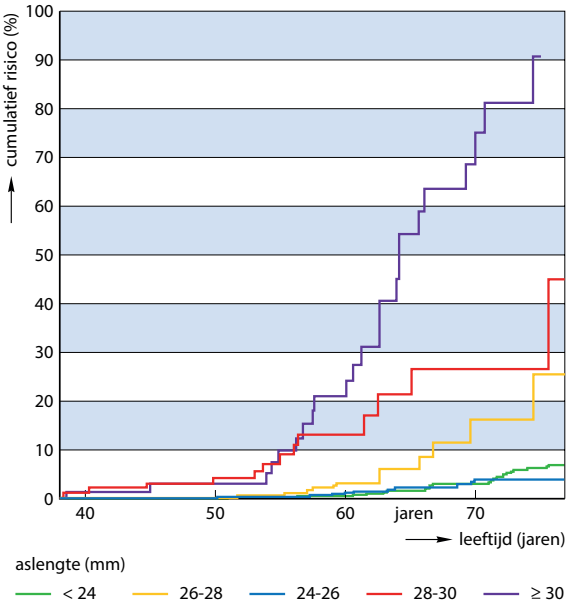
Figuur 1. Normaal zicht (rechts) en bijziendheid (links).

PATHOLOGISCHE MYOPIE

Het dragen van een bril kan vervelend zijn, maar dat is niet het grootste probleem. Het langer worden van het oog bij myopie heeft tot gevolg dat de structuren aan de achterkant, het netvlies, het vaatvlies en de sclera, aanzienlijk dunner worden. Deze verdunning geeft aanvankelijk nog weinig problemen, maar kan opspelen bij veroudering. De sclera (buitenste witte ooglaag) bestaat voornamelijk uit collageen, en als dit zijn stevigheid verliest kan een uitbochting (stafyloom) ontstaan. Dit verhoogt het risico op netvliescomplicaties zoals myope maculadegeneratie, maculagaten en retinoschisis (splijting van het netvlies). Andere complicaties die kunnen ontstaan, zijn netvliesloslatingen, openkamerhoekglaucoom en staar (figuur 2). Voor het overgrote deel van deze aandoeningen is op dit moment geen goede behandeling beschikbaar en geldt dat slechtziendheid of zelfs blindheid onvermijdelijk is. Hoe langer het oog en dus hoe hoger de graad van myopie, des te groter de kans op pathologie. Ter illustratie: het risico op ernstige slechtziendheid of blindheid is 25,4% bij een aslengte van 26-28 mm (–6 tot –10 dioptrie) en dit loopt op tot 90,6% bij een aslengte van 30 mm of meer (≤ –15 dioptrie). Voor alle hoog myopen samen geldt dat een op de drie in de loop van het leven ernstig slechtziend of blind wordt.[6] Een dilemma is dat de ooggroei plaatsvindt in de jeugd, terwijl de problemen doorgaans pas na het veertigste levensjaar optreden. Preventie of vertraging van myopieontwikkeling op de kinderleeftijd is dus erg belangrijk.



Figuur 2. Complicaties bij hoge myopie: myope maculadegeneratie (a,b), hypopigmentatie (c) en openkamerhoekglaucoom (d).



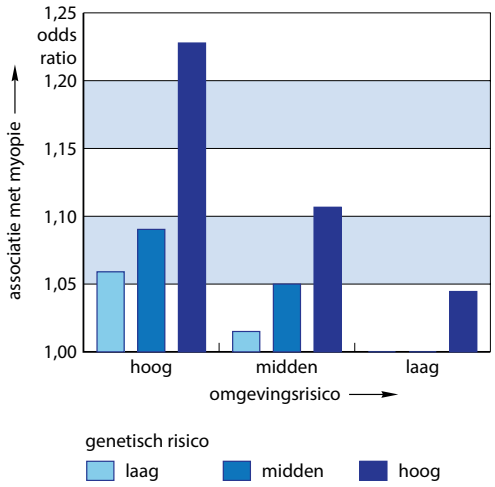
Figuur 3. Risico op slechtziendheid of blindheid voor alle leeftijden per aslengtecategorie.[6]

OORZAKEN VAN MYOPIE

Genetica

Bij myopie kunnen genetische factoren een rol spelen. Er is een duidelijke familiaire predispositie en inmiddels zijn er meer dan vijfhonderd genetische risicovarianten voor refractie geïdentificeerd. De meeste daarvan hebben op zichzelf een klein effect, maar gezamenlijk verklaren ze ongeveer 18% van de variatie in refractie.[7] Er zijn echter ook vormen van hoge myopie die worden veroorzaakt door een enkele genetische variant met een groot effect. We onderscheiden hierin retinale dystrofieen, bindweefselaandoeningen, monogenetische oorzaken van myopie en overige syndromale aandoeningen. Hoge myopie kan een (eerste) symptoom zijn bij een retinale dystrofie (*RPGR*-gerelateerde retinitis pigmentosa, congenitale stationaire nachtblindheid). Ook bindweefselaandoeningen zoals het marfan- en het sticklersyndroom gaan vaak gepaard met hoge myopie.[8] Daarom is het bij kinderen met hoge myopie van belang om alert te zijn op symptomen die passen bij een retinale dystrofie (nachtblindheid of verminderd kleuren zien), bindweefselaandoeningen (hypermobiliteit, skeletafwijkingen en cardiovasculaire afwijkingen), bijkomende afwijkingen

(verstandelijke beperking) en/of dysmorfe kenmerken. Voor kinderen geldt in principe de vuistregel dat wanneer de myopierefractie hoger is dan de leeftijd (bijv. –6 dioptrie op 5-jarige leeftijd), erfelijkheidsonderzoek en/of verwijzing naar de klinisch geneticus wordt geadviseerd.



Figuur 4. Erfelijke en omgevingsfactoren en aanwezigheid van myopie.[9]

Educatie en dichtbijwerk

De snelle toename in de prevalentie van myopie wordt vooral veroorzaakt door veranderingen in omgevingsfactoren. Al in het begin van de negentiende eeuw werd beschreven dat myopie vaker voorkwam bij mensen uit de hogere sociaal-economische klasse.[10] Vooral educatie blijkt in studies onder ouderen een sterke en consistente risicofactor voor myopie te zijn.[11] Inmiddels is duidelijk dat deze relatie kan worden verklaard door het langdurig dichtbij kijken (< 50 cm) tijdens studeren.[12] Ook kinderen die voor hun plezier veel boeken lezen, zijn vaker myoop.[13] Een waarschijnlijke oorzaak is dat bij dichtbij kijken het brandpunt in de periferie achter het netvlies valt (perifere hyperope defocus), waardoor het oog geneigd is te groeien. Studies onder jongere generaties laten zien dat de associatie met educatie minder sterk aan het worden is.[11] Basisschoolkinderen van families uit een lagere sociaal-economische klasse in Rotterdam zijn zelfs vaker myoop.[14] De huidige trend van toenemend schermgebruik lijkt daarin een rol te spelen. Veelvuldig gebruik van de computer op zeer jonge leeftijd verhoogt het risico op myopie en recent onderzoek laat zien dat ook smartphonegebruik het risico verhoogt.[13,15] Niet alleen de duur, maar ook een korte leesafstand is een belangrijke factor; het advies voor kinderen is dan ook om films en games liever op grotere afstand te bekijken dan via schermen die men in de hand houdt.

Buitenspelen

De voordelen van buitenspelen als interventie zijn verminderde incidentie van myopie, afname van de progressie van myopie en afname van de aslengtegroei. Meerdere gerandomiseerde studies zijn uitgevoerd waarbij kinderen op 'interventiescholen' langere schoolpauzes kregen en werden gestimuleerd om ook na schooltijd meer naar buiten te gaan. Het bewijs is zeer overtuigend: in alle studies werden de kinderen op de interventiescholen minder vaak myoop dan kinderen op de reguliere scholen.[16,17] Een belangrijke verklaring voor het beschermende effect is de hoge lichtintensiteit. Binnen is de lichtintensiteit meestal 500 lux of minder, terwijl dit buiten varieert van 1000 lux op een bewolkte dag tot 100 000 lux op een zonnige dag. Het effect van buitenspelen op myopie treedt op vanaf een lichtintensiteit van ongeveer 1000 lux, en dit wordt al bereikt door buiten te spelen in de schaduw of met een zonnebril of pet op in de zon.[17] Wereldwijd wordt aan alle kinderen geadviseerd om twee uur per dag buiten te spelen om myopie te voorkomen. Onze eigen studies onder Rotterdamse kinderen laten zien dat dit helaas maar gemiddeld één uur per dag is, en ook elders in de wereld worden de twee uur maar zelden bereikt.[13]

De 20-20-2-regel

Neem na elke 20 minuten dichtbijwerk 20 seconden pauze door in de verte te kijken.
Daarnaast is het belangrijk om dagelijks 2 uur naar buiten te gaan.

BEHANDELING

Leefstijladvies is voor alle kinderen aanbevolen om myopie te voorkomen of de progressie ervan tegen te gaan. Sommige kinderen hebben echter moeite om zich aan de leefstijlregels te houden of hebben sterke erfelijke factoren als oorzaak van de myopie. Wanneer myopie ontstaat voor het twaalfde levensjaar, of kinderen sterk progressieve myopie hebben (> 0,5 dioptrie per jaar) wordt een interventie aanbevolen. Momenteel worden drie interventies toegepast in Nederland; atropine oogdruppels, multifocale zachte contactlenzen en orthokeratologie (ortho-K lenzen, bijvoorbeeld Nachtlenzen©). Van deze drie interventies zijn atropine oogdruppels het effectiefst; die kunnen in hoge doses 75% reductie van de aslengtegroei bewerkstelligen.[18] Elke dag een druppel atropine (0,01-1%) in het oog verhoogt de dopaminespiegels in het oog, wat de ooggroei vertraagd.[19,20] De hoge dosis kan wel fotofobie en leesproblemen geven; hiervoor worden multifocale meekleurende glazen voorgeschreven. Laag-gedoseerde atropine geeft minder bijwerkingen, maar heeft ook een minder effectieve werking. Multifocale zachte contactlenzen en ortho-K lenzen remmen myopieprogressie door

hun optische projectie van lichtstralen op het netvlies waardoor het oog, net als bij atropine, minder prikkels tot groei krijgt. Zij hebben een lagere effectiviteit dan hoog-gedoseerde atropine en kunnen ooginfecties veroorzaken. Daarom zijn zij geschikter voor kinderen boven de 12 jaar bij wie de myopieprogressie niet zo sterk is. Wij raden aan kinderen van 12 jaar en jonger te verwijzen naar een in myopie gespecialiseerd team van oogarts en orthoptist. Veel ziekenhuizen hebben inmiddels zo'n team. Zij zullen samen met het kind en de ouders besluiten welke therapie het best past. De volledige diagnostiek voor een kind met kans op hoge myopie is te vinden in tabel 1.

Tabel 1. Klinische diagnostiek van een kind met forse progressie van myopie op jonge leeftijd.

medische voorgeschiedenis	leeftijd van ontstaan van de myopie leefstijlfactoren: dichtbijwerk en buitenspelen visus, nachtblindheid, kleurenblindheid gehoorverlies schisis (incl. Pierre Robinsequentie) hypermobiliteit en skeletafwijkingen cardiovasculaire afwijkingen (aortawortelditatie of dissectie) ontwikkelingsachterstand, verstandelijke beperking familiegeschiedenis: driegeneratiestamboom met speciale aandacht voor (hoge) myopie, gehoorverlies, schisis, cardiovasculaire afwijkingen, visusproblemen en/of blindheid
oogheelkundig onderzoek	visus cycloplegische refractie biometrie inclusief aslengtemeting fundoscopie eventueel elektroretinografie en beeldvorming van het netvlies (eg. OCT)
lichamelijk onderzoek	dysmorfieën (midface hypoplasia, marfanoïde habitus) lengte; span-/lengteratio *wrist sign*, *thumb sign* beighton-hypermobiliteitsscore skeletafwijkingen (pectusafwijkingen, aplasia cutis)
aanvullend onderzoek	in geval van een herkenbaar syndroom: gerichte DNA diagnostiek in geval van niet herkenbaar syndroom of bredere differentiaal diagnose: overweeg next-generation sequencing of whole-exome sequencing. overweeg verwijzing naar klinisch geneticus
differentiaaldiagnose	'gewone' myopie monogenetisch geïsoleerde hoge myopie (*ARR3*) bindweefselaandoening (marfan-, stickler-, knoblochsyndroom) retinale dystrofie (*RPGR*-gerelateerde retinitis pigmentosa, congenitale stationaire nachtblindheid) andere syndromale oorzaak

TOT SLOT

Myopie is een groeiend probleem. Inmiddels is ongeveer de helft van alle jongvolwassenen in Europa myoop; in 2050 zal naar verwachting 10% hoog myoop zijn. De jongvolwassenen met hoge myopie van nu zullen zich pas over tientallen jaren met netvliescomplicaties bij de oogarts presenteren. Om een grote golf van slechtziende myopiepatiënten te voorkomen, moet nu actie worden ondernomen. Op het gebied van de jeugdgezondheidszorg is advies ten aanzien van de leefstijl het belangrijkste: langdurig dichtbijwerk beperken, zowel op papier als digitaal, en zo veel mogelijk buitenspelen. Als myopie op jonge leeftijd (≤ 12 jaar) ontstaat of snel progressief is, kunnen atropine-oogdruppels, multifocale contactlenzen of ortho-K-lenzen worden voorgeschreven om verdere progressie te remmen. Wanneer de myopierefractie hoger is dan de leeftijd, dan is dat een indicatie voor erfelijkheidsonderzoek.

Alleen als kind- en oogzorgverleners, onderwijskundigen, jeugdartsen en huisartsen zich allen bewust zijn van de gezondheidsrisico's die myopie met zich meebrengt, kan er genoeg draagvlak komen voor het op grote schaal toepassen van tegenmaatregelen.

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Natuurlijk naar buiten!

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Accepted in TSG

Meer buiten spelen maakt kinderen gezonder! Een actieve leefstijl is van groot belang voor een optimale groei en ontwikkeling van kinderen. De beperkingen als gevolg van het coronavirus maken dit extra zichtbaar. Het professionele netwerk 'Zicht op Buiten' bracht de gevolgen van te weinig buiten zijn en beweging voor de gezondheid van kinderen en jongeren in kaart, op het gebied van visus, motoriek, houding, overgewicht, slaap en psychosociale gezondheid.[1, 2] We bevelen sterk aan om twee uur per dag naar buiten te gaan voor gezonde kinderogen, waarvan tenminste 1 uur matig-intensief bewegen om uithoudingsvermogen, spieren en botten te versterken. Andere leefstijl maatregelen zijn het verminderen van sedentair gedrag en regels over schermgebruik evenals regelmatig afwisselen van zittende activiteiten.

Outdoors of course!

Outdoor play makes children healthier! An active lifestyle is particularly important for optimal growth and development of children. Restrictions due to the Corona virus make this more apparent. The professional network 'View Outside' collected the lifestyle consequences for visual, motoric, postural, weight, sleep and psychosocial youth health. We strongly recommend spending two hours a day outdoors of which a minimum of one hour should be at least moderately intensive exercise. Other lifestyle measures are reducing sedentary behavior, rules on screen use and regular change of activities when sedentary.

BUITENSPELEN

Buitenspelen hangt sterk samen met lichamelijk actief zijn en is daarom een belangrijke factor voor een gezonde ontwikkeling van kinderen.[3] Wereldwijd spelen kinderen steeds minder buiten en in Nederland blijkt uit onderzoek van Jantje Beton in 2018 dat 53% van de kinderen in hun vrije tijd vaker binnenspelen dan buiten.[3, 4] Er was de laatste vijf jaar een toename van het aantal kinderen dat minder buiten speelt dan dat zij zouden willen (19% versus 28% qua behoefte). Drie- en zesjarige kinderen uit de Rotterdamse studie Generation R zijn gemiddeld 1,5 uur per dag buiten, op negenjarige leeftijd is dat gedaald naar nog maar 1 uur per dag.

Tabel 1. Gezondheidsgevolgen

Myopie (bijziendheid)	De helft van alle jongvolwassenen heeft myopie. Kinderen die veel dichtbij kijken (schermgebruik, lezen o.a.) én weinig buiten zijn, hebben een veel hoger risico om myopie te ontwikkelen dan kinderen die veel dichtbij kijken maar ook voldoende buiten spelen.[1, 5]
Overgewicht	Dertien procent van de kinderen heeft overgewicht, waarvan 2% ernstig (obesitas). Regelmatige lichamelijke activiteit van tenminste matige intensiteit, zoals bijvoorbeeld buitenspelen verlaagt de body mass index (BMI) en vetmassa bij kinderen met overgewicht en obesitas.[6]
Motorische ontwikkeling	Motorische fitheid onder kinderen is in de afgelopen decennia afgenomen. Kinderen die meer tijd binnen zitten en besteden aan tv-kijken hebben over het algemeen een slechtere aerobe fitheid.[6, 1]
Houding, rug- en nekklachten	Lage rugklachten komt voor bij 34% tot 46% van de kinderen en jongeren en dit lijkt toegenomen. Extreem veel en verkeerd zitten en gebogen op schermpjes turen gaat gepaard met ongelijkmatige belasting van de wervelkolom, leidend tot houdingsverval.[7]
Slaapproblemen	Slaapproblemen komen voor bij 20-30% van de peuters en kleuters, en bij 7% tot 36% van de adolescenten. Recente studies hebben laten zien dat kinderen die overdag meer buiten zijn, beter en langer slapen.[8]
Psychosociale problemen	De laatste decennia zien we een toename van kinderen, adolescenten en jongvolwassenen met angststoornissen, depressieve gevoelens, suïcidale gedachten, hulpeloosheid en narcisme.[9] Er is steeds meer bewijs dat beweging niet alleen goed is voor lichamelijke gezondheid, maar ook voor mentale gezondheid.[10]

Het professionele netwerk 'Zicht op Buiten' houdt zich al langer bezig met leefstijl verandering bij de jeugd specifiek gericht op de toename van beeldschermgebruik.[2] Dit netwerk bracht de gevolgen van te weinig beweging en buiten zijn voor de gezondheid van kinderen en jongeren in kaart, op het gebied van visus, motoriek, houding, overgewicht, slaap en psychosociale gezondheid (Tabel 1). Deze groep bestaat uit onder anderen een oogarts-epidemioloog, orthoptist, jeugdartsen, kinderartsen, jeugdverpleegkundige, orthopeed, bewegingswetenschapper-epidemioloog, gezondheids-wetenschappers en psychologen. In november 2020, bood het netwerk een 'White Paper' aan de secretaris generaal van het ministerie van VWS om aandacht te vragen voor de gezondheidsgevolgen.[1] In dit forum-artikel

vatten we de gevolgen en praktische adviezen samen. We vragen tevens alle maatschappelijk betrokkenen om bij te dragen aan de oproep om kinderen gedurende twee uur buiten te laten zijn en daarmee binnen zitten en overmatig schermgebruik te verminderen.

LEEFSTIJLADVIEZEN

'Voorkomen is beter dan genezen', dus meer bewegen, zoals meer buitenspelen, maar ook meer bewegend(er) leren op school, heeft een positief effect op bovenstaande gevolgen. In Nederland heeft de Gezondheidsraad een beweegrichtlijn opgesteld voor volwassenen en kinderen. Deze komen overeen met die van de Wereldgezondheidsorganisatie WHO voor kinderen van 5 tot 17 jaar.

1: Minimaal 60 minuten per dag matig tot zwaar lichamelijke activiteit per dag.
2: Meer beweging dan 60 minuten per dag levert extra gezondheidsvoordelen op.
3: Minimaal drie keer per week spier- en botversterkende activiteiten.

De Jeugdgezondheidszorg (JGZ)- Richtlijn Houding en Beweging adviseert een gezonde afwisseling van zittende activiteiten. Het versterkt de nek en rugspieren. Ook wordt geadviseerd om elke dag buiten te spelen, ook als het regent, en om het beweegadvies van de Gezondheidsraad te volgen. De myopie richtlijn geeft het advies voor kinderen de 20-20-2 regel te volgen: na 20 minuten dichtbij kijken, 20 seconden in de verte kijken, plus 2 uur per dag naar buiten.[5] Uit een peiling van het Oogfonds blijkt dat kinderen deze regel duidelijk vinden en makkelijk onthouden.[1] De JGZ-richtlijn Gezonde Slaap adviseert om kinderen iedere dag buiten te laten spelen, zodat zij voldoende bewegen en daglicht zien. Hierdoor vallen kinderen 's avonds sneller in slaap en slapen ze dieper. Ook het spelelement in buitenspelen draagt bij aan een gezonde ontwikkeling. Kinderen die vaker buitenspelen hebben daardoor betere sociale vaardigheden. Voor adolescenten adviseert de richtlijn om elke dag naar buiten te gaan, omdat blootstelling aan zon- of daglicht helpt om de biologische interne klok in de pas te houden. Daarnaast is het advies om regelmatig te bewegen. Dit kan zelfs ingezet worden als behandeling bij depressie en regelmatig joggen heeft een positief effect op adolescenten met depressieve symptomen.[10]

Samenvattend**,** weinig buitenspelen, overmatig dichtbij kijken en langdurig beeldschermgebruik bij kinderen leveren op de korte en lange termijn gezondheidsproblemen op. De werkingsmechanismes achter de negatieve gezondheidseffecten op de ogen, het gewicht, de motoriek, het bewegingsapparaat, slaapkwaliteit, en psychosociale gezondheid worden steeds duidelijker. Dat brengt ons tot de conclusie dat de verandering in leefstijl zich vertaalt in een toename van aandoeningen die later uitmonden in chronische ziektelast. Dit zal ook meer ziektekosten met zich meebrengen. Wij vrezen dat deze gezondheidseffecten, door de grote

schaal waarop ze zich voordoen, ook gevolgen zullen hebben voor de kansen van opgroeiende jongeren om duurzaam in de maatschappij te participeren in onderwijs, sport, en op de arbeidsmarkt. Als groep professionals willen wij onze zorgen uitspreken over de veranderende leefstijl en pleiten wij voor bewustwording bij iedereen die zich bezig houdt met de doelgroep jeugd.[2]

VERTALING NAAR DE PRAKTIJK EN KANSEN

Duurzame verandering kan alleen als we als volwassenen het goede voorbeeld geven én onze sociale en fysieke omgeving veranderen. Professionals in de gezondheidszorg kunnen individueel adviezen geven, maar voor maatschappelijke impact is veel meer nodig. We willen de focus leggen op positieve gezondheid en zeker als het gaat om kinderen gezond gedrag benadrukken, zoals buiten zijn, buiten spelen, bewegen en veel afwisseling bij beeldschermgebruik.

De meest favoriete plaatsen van kinderen om buiten te zijn, zijn het schoolplein, de tuin en natuur of bos.[4] Een veilige speelomgeving is hierbij een voorwaarde; gemeenten kunnen hierin een rol spelen. Integraal beleid waarbij er samenwerking is tussen onderwijs, zorg, gemeenten en de landelijke overheid werkt, zoals met de JOGG-aanpak en de Gezonde School aanpak. De gemeente Venray heeft een leefstijlakkoord waarbij er bijzondere verbindingen zijn tussen sport en andere domeinen met het doel de leefstijl van de jeugd preventief te verbeteren. Een gezonde leefomgeving wordt ook gestimuleerd bij andere gemeentes zoals de regio IJsselland en zestien Zuid-Limburgse gemeenten. Daarnaast zijn er de afgelopen jaren regelmatig regionale campagnes gevoerd om beweging en buiten spelen te stimuleren, zoals 'gratis bewegen, gewoon doen' van de gemeente Groningen.

Verschillende organisaties en sectoren proberen op hun eigen gebied bij te dragen aan een gezonde en activerende omgeving voor jeugdigen. Bijvoorbeeld het Kenniscentrum Sport en Bewegen en het Nederlands Centrum Jeugdgezondheid, die samen bewegingsvaardigheden bij jonge kinderen van 0-4 jaar gaan stimuleren op consultatiebureaus. In het onderwijs komt steeds meer aandacht voor bewegend(er) leren. Maar we vragen ons af of de groeiende problemen die wij hebben geschetst bij iedereen goed op het netvlies staan en meer nog, of voldoende mensen en organisaties zich richten op preventie en oplossingen met duurzame impact. In de landelijke nota gezondheidsbeleid 'Gezondheid breed op de agenda' 2020-2024, doet het ons ons deugd dat er aandacht is voor de fysieke en sociale omgeving. Hiermee wordt de prioritering in de publieke gezondheid door het Rijk aangegeven. De vertaling naar de praktijk via de lokale nota's jeugdbeleid is nu volop in gang en er liggen kansen om de

leefomgeving niet alleen te veranderen maar ook gedrag te beïnvloeden. Wetenschappelijke erkende interventies zijn beschikbaar (zie de Interventie database van het RIVM Loket Gezond Leven), maar er is veel meer nodig.

Het netwerk 'Zicht op Buiten' is bezig om maatschappelijke bewustwording te creëren door in de Buitenspeelweek van 2021, een webinar te organiseren voor alle beleidsadviseurs. In het najaar volgt een webinar voor ouders en onderwijs. Maar het netwerk heeft hulp nodig bij de volgende stappen. Wat kunnen we nog meer doen om het gedachtengoed breed te verspreiden om gezond gedrag (twee uur per dag buiten zijn en gezond beeldschermgebruik) te realiseren?

OPROEP

Wij, het netwerk 'Zicht op Buiten', doen daarom een oproep aan alle betrokkenen, ouders en andere opvoeders, individuele medewerkers en organisaties in het onderwijs, gezondheidszorg, sport, werkgevers en werknemers, gemeenten en andere overheden om mee te denken over de volgende te nemen stappen.

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Part VII

General discussion and appendices

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General discussion

GENERAL DISCUSSION

The aim of this thesis was to investigate the development of myopia in childhood and adolescence, and in particular the association with lifestyle factors. The prevalence of myopia has increased so rapidly in the last decades that it is unlikely to be caused by genetic factors alone. Influence by the new lifestyle in children, from being mostly outdoors to being mostly indoors is more likely. This general discussion will highlight the most important findings of the chapters, the implications for society and future directions for research and the methodological considerations.

Burden of disease

In **Chapter 3**, we investigated the prevalence of spectacle wear in 3 to 7 year old children, and whether their spectacle wear was due to myopia. Among all spectacle wearers, around 30% of the Generation R participants at age 6 and of the Rotterdam Amblyopia Screening Effectiveness Study (RAMSES) participants at age 7 had myopia. In **Chapter 4**, myopia prevalence increased from 2.5% to 11.5% and 22.5% in respectively 6, 9 and 13 year old children in Generation R. In the adults of the Rotterdam Study, myopia prevalence increased from 22.5% in birth years <1920 to 39.2% in birth years ≥1940; a generation effect with a 74% increase within a 40 years' time frame. As the prevalence of myopia increased whereas hyperopia decreased with increasing birth year in a large meta-analysis of European data, this indicates a general shift towards myopia in the whole population.[1] Most compelling are the results from studies in China. For example, the prevalence of myopia in young Chinese adults increased from 79.5% in 2001 to 87.7% in 2015, and high myopia from 7.9% to 16.6% respectively. As most of the participants were already myopic in 2001, 'only' a 10% increase in myopia prevalence was observed, but a 110% increase in high myopia prevalence over a 15 years' time frame.[2] A cross-sectional study from Wang et al (2021) in which yearly vision screenings were performed in 6 to 13 year old children from 2015 to 2020 was discussed in **Chapter 5**.[3] In the year 2020, after 5 months of home confinement due to the COVID-19 pandemic, an incredible increase in myopia prevalence of 40% to 400% was observed in the 6 to 8 year olds.[4] Similar results were seen in 5 to 18 year old children with progressive myopia from Argentina.[5] As many Dutch high school children – by the time of writing this discussion – are still receiving online schooling, the prevalence and severity of myopia in the Netherlands is expected to increase tremendously in the upcoming years.

Early onset myopia is problematic, because it will likely lead to higher myopia during adolescence or adulthood.[6, 7] Low, medium and high myopia show an increased risk of myopic macular degeneration, retinal detachment, posterior subcapsular cataract and open angle glaucoma as described In **Chapter 2**. Since all these patients need to be treated by ophthalmologists, the

health expenditure due to myopia is on the rise.[8] The risk of complications and irreversible visual impairment increased with a higher myopia degree, longer axial length and older age.[9] The risk of visual impairment in individuals with axial length of >28 mm or spherical equivalent ≤-10 diopter started to increase already from the age of 55, therefore resulting in productivity loss of the working – generally higher educated - population.[10] The lifetime risk of visual impairment was 25% for axial lengths of 26-28 mm, and 90% for axial lengths of >30 mm.[11] Reducing as many diopters of refractive error or mm of axial length as possible in childhood is important, also when a degree of high myopia has already been reached.[12]

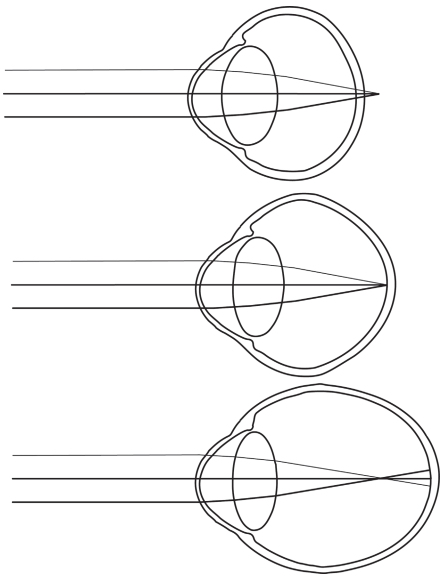

Figure 1. Refractive state of a hyperopic eye (A) which grows towards emmetropia (B) during the emmetropization process. When emmetropia is reached too early, the eye will continue to grow towards myopia (C).

Etiology

Children are born with a moderate hyperopic refraction following a Gaussian distribution, which decreases and changes towards a narrower leptokurtic distribution during the first year of life.[13-15] This active process is called emmetropization, and is largely finished by the age of 6 years.[16] The axial length is around 17 mm at birth and increases vastly to about 20 mm around the age of one year.[13, 14] The eye then continues to grow with about 0.4 mm per year to 22 mm at the age of 5 years, and slowly stabilizes to around 23.5 mm in adulthood.[16, 17] Corneal power is around 47 diopter at birth and decreases in the first year of life. It then remains relatively stable and is therefore not considered as a major player in myopia development.[13, 16-19] Lens

thickness is around 3.75 mm, and lens power around 44 diopter at birth, they both slightly decrease until early adolescence.[13, 14, 20, 21] Children with myopia generally have thinner and less powerful lenses than emmetropic children, but the direction of causality is still debatable.[22-24] Children with larger axial length or axial length corneal radius ratio at young age are more likely to develop myopia.[17] Likewise, children with early onset myopia progress faster than those with emmetropia or hyperopia.[6]

Near work

A worldwide increase in primary, secondary and tertiary educational enrolment has been observed from 1950 to 1970 with higher educational enrolment rates in higher income countries.[25] In **Chapter 4**, we showed that the percentage of higher educational level increased from 5.5% in the birth year group <1920 to 26.5% in the birth year group ≥1940 and a strong association with myopia was found.[26-29] Males were more often myopic in the adult cohort because they were higher educated than females, while girls were more often myopic in the child cohort, potentially because they read more often than boys. As relatively new near work activities arise, such as computer and smartphone use, the effect of education on myopia may slowly fade out. Computer use, reading time, number of books read per month and reading distance were associated with myopia as shown in **Chapters 4, 6 and 9**. In addition, ≥20 minutes of continuous smartphone use was associated with a more myopic refractive error among Dutch teenagers in **Chapter 7**. More studies recently identified an association between screen time and myopia.[30, 31] Performing lots of near work activities will likely become part of daily life in all populations, from the more affluent to socioeconomic disadvantaged members of society. As indicated in **Chapter 8**, more computer use and higher myopia incidence were observed in 6 to 9 year old children from socioeconomic disadvantaged families and children with non-Dutch background. Such shifts in disease risk from higher to lower socioeconomic classes have been seen before in body mass index and weight.[32, 33] For example, lower socioeconomic position was associated with lower weights in child cohorts born before 1970, and higher weights in child cohorts born in 2001.[32] Without lifestyle interventions in particular focusing on these groups, myopia may become a disease of the lower socioeconomic groups in the future. Moreover, during the COVID-19 pandemic, increased screen time and decreased physical activity was observed in children during lockdowns in different countries.[34-36] These changes - on top of the already considerable amount of time spent on near work - suggest that myopia development will increase further in the upcoming years.[4, 5]

Outdoor exposure

In the last decades, children gradually started to play less time outdoors.[37] From 1982 to 2002, time spent on outdoor activities and sports decreased with respectively 50% and 25% in US children.[38] Also among Dutch children, daily outdoor play decreased from 20% in 2013 to 14% in 2018.[39] New generations of children play less time outdoors than their parents or grandparents did when they were young.[39, 40] Several randomized controlled trials have been performed in Asia to study the association between outdoor exposure and myopia. Schoolchildren who were encouraged to spend an additional 40 to 80 minutes outdoors during school time had 4.8% to 9.2% less myopia incidence, and 0.05 mm/year less axial elongation after one year.[41, 42] The 'treatment' effect was 0.23 diopter and 0.15 mm axial elongation in children with myopia at baseline, which is comparable with optical or low dose atropine treatment.[43-45] A recently published study among >10,000 9 to 11 year old children from Taiwan showed that outdoor exposure was associated with myopia incidence as well as with myopia progression; evidence that lifestyle advice still applies after myopia has been developed.[46] Outdoor exposure not only reduces myopia incidence or progression, it also moderates the association between near work and myopia as presented in **Chapter 6**.[47, 48] Depending on the intensity level of near work activities that a child performs, more or less outdoor exposure is needed to compensate for. Dose-response analyses of trials and observational studies showed that 7 to 10 hours additional outdoor exposure per week was needed to obtain a 50% reduction in myopia incidence as compared to the control group.[49, 50] As 9 year old children from the Generation R study spent on average only 1 hour per day outdoors,[48, 51] outdoor time should be doubled in order to obtain a 50% reduction.

Biological mechanisms

The mechanisms through which increased time spent on near work activities and lack of outdoor exposure may alter axial growth still need to be unraveled. Near work is thought to increase axial growth through a mechanism called peripheral hyperopic defocus. Due to looking at an object close by, the focal plane of light rays falls behind the retina in the periphery, thereby creating a hyperopic defocus which triggers the eye to grow towards the focal plane. Evidence from different animal models showed that an artificial hyperopic defocus, induced by concave lenses, lead to choroidal thinning and axial growth, whereas myopic defocus lead to choroidal thickening and reduction of growth.[52-54] Similar results were observed in young adults and children after 1-2 hours of hyperopic or myopic defocus.[55-58] This mechanism is the basis of optical interventions against myopia progression, such as multifocal contacts or orthokeratology.[59-61] Outdoor exposure most likely prevents myopia (progression) because of the higher illuminance outdoors. High light levels trigger dopamine release and activation of dopamine receptors in the retina, which may inhibit ocular growth.[62, 63] Alternatively, the chromaticity of light may influence eye growth by a wavelength-specific

defocus.[64] Animal models showed that short wavelength light reduced myopia development, while long wavelength light increased myopia development in chicks and guinea pigs.[65-69] However, reversed associations were found in rhesus monkeys and tree shrews.[70, 71] Only two studies have been performed in humans, both suggesting that short wavelength light (ultra violet 360-400 and blue light 456 nanometer) may reduce myopia development.[67, 72] Since morning sunlight contains more short wavelength light than evening sunlight, this may imply that outdoor play would be more beneficial against myopia development in the morning.

Risk profiling

Myopia control is currently mainly focused on reducing the rate of progression, but preventing the onset of myopia is an even more valuable target.[73] Lifestyle interventions are needed for those who are at risk to develop myopia. Children from parents with myopia are more likely to develop myopia themselves.[74-76] In **Chapter 9**, we found that parental myopia was associated with increased genetic risk as well as increased environmental risk, which suggests that environmental risk factors for myopia run in myopic families. This is underscored by a significant correlation in outdoor time and physical activity between parents and children.[72, 77, 78] The discriminative value of parental myopia was 0.67, not statistically different from genetic or environmental risk scores. Combining parental myopia with gene-environment interaction improved the discriminating value to 0.73.[51] Other prediction models in different ethnic cohorts showed that previous eye measurements - refractive error or ocular biometry - are the best predictors for myopia incidence.[79-81] In **Chapter 10**, we found that both genetic and environmental risk factors for myopia have widely differing impacts in different individuals depending on where they were on the refractive error distribution. We observed that the differences in effect sizes, higher effects in the most myopic and hyperopic groups, were larger in the older children.[82] This suggests that in individuals whose emmetropization compensation limit is surpassed, genetic and environmental risk factors could lead to greater effects. Lifestyle changes may be particularly beneficial for children destined to reach the extreme myopic arm of the refractive error distribution by adulthood.[83, 84]

Public health implications

With the current knowledge about the causes of myopia in childhood, we now require a consequential approach by focusing on health optimization.[85, 86] From a public health point of view, discouraging children to read counteracts with the already decreasing reading ability among Dutch children.[87] As mentioned in **Chapter 12**, replacing non-educational near work, such as screen time, by outdoor play or outdoor sports should be the main target. At least two hours of outdoor exposure per day to prevent myopia is the international consensus.[88-90] Achieving this is easier said than done. Successful interventions to increase outdoor play should be tailored to the target group, easily incorporated into the daily routine and focus on

changing the parents practices in order to change the children's behaviour.[91] Since targeting multiple systems in ecological interventions seem more effective than traditional individual based interventions,[92] family, neighborhood, childcare and school interventions, as well as the responsibility of (youth) healthcare professionals will be discussed in the following paragraphs.

Family interventions

Most parents have limited understanding of the causes of myopia, and do not fully recognize the associated risks of future vision loss.[93] However, parent's attitudes and behaviors, such as paying attention to their children's vision and limiting their children's electronic devices, were associated with a decreased risk of myopia.[94] Parental support in being active increased the physical activity of a child, which provide opportunities for the role of the parent in increasing the child's outdoor play.[95] According to Clark and Dumas (2020) a structural change in the priority of outdoor play over other activities, and acceptance of unsupervised activities would be needed, because most parents face issues such as safety concerns and the child's level of independence when the child plays in public open spaces.[96-98] Family-based interventions to increase outdoor play are scarce and more research in particular in the context of myopia prevention is necessary.[99] Regarding digital near work, many mobile applications limiting smartphone use have been developed, although most of them target adults.[100-103] Effective apps for example provide messages telling the user that he or she had hit the daily time limit, or contain a lockout task before the smartphone can be used.[100, 101] A group-based intervention app was more effective than an individual-based intervention app in limiting smartphone use.[102] In one study, limiting smartphone use was considered as a family activity in which a virtual public space was provided including self-monitoring, a use-limiting tool and a family dashboard. This enabled more two-way interactions between adults and children, and smartphone use was less defined by hierarchical authority arrangements.[103] The long term effects of apps in limiting smartphone use still need to be investigated as they might be prone to a novelty effect, but they seem promising.

Neighborhood interventions

Safety concerns of parents in mainly deprived neighborhoods illustrate the need to improve the neighborhood environment to encourage outdoor play. Neighborhood characteristics have been associated with outdoor play.[104, 105] For example, providing attendants at playgrounds to increase safety in low income neighborhood resulted in increased outdoor play in children.[106] Another inexpensive and effective strategy to increase outdoor play is to close the streets for traffic during weekend or afternoons.[107, 108] Both interventions have not been investigated in the context of myopia yet, and deserve more attention. In **Chapter 8**, we found that living close to a newly introduced physical activity space in Rotterdam was associated with 1.3 hours per week increased outdoor exposure only in children from families with lower maternal

education, but the physical activity spaces did not inhibit myopia development. Providing safety and guidance at physical activity spaces or playgrounds seems to be important to increase outdoor play among children. Local initiatives, or collaborations with childcares and schools are needed to accomplish this. Finally, increased residential greenness has been associated with a decreased prevalence of myopia in two studies.[109, 110] Both studies had some limitations as incidental spectacle wear was used as a proxy for myopia in the first study, and analyses were cross-sectional in the second study.[109, 110] However, the findings were confirmed by other studies in which an association between green spaces and increased physical activity or outdoor play or decreased screen time was reported.[111-113] Providing more green spaces, especially in deprived areas, seems to be an effective public intervention to prevent myopia in childhood.

School and kindergarten interventions

An effective example of a school-based trial is one that is performed at primary schools in Taiwan.[43] The intervention schools participated in a recess outside classroom program, which consisted of 40 minutes outdoor play during recess at school in both the morning and afternoons. Outdoor-oriented school activities were promoted and out-of-school components were included such as outdoor activities with family and outdoor learning assignments, the parents received education and the children were encouraged by certificates and prize rewards using a points system. This comprehensive intervention resulted in 70 minutes/week more outdoor exposure in the intervention group, and 50% of them had >11 hours/week outdoors time compared to only 23% of the control group. Also in the Netherlands, increasing interest is paid on physical activity and health as illustrated by many national health policies such as The National Sports Agreement and The National Health Policy Memorandum (*Nationaal Sportakkoord* and *Landelijke nota gezondheidsbeleid 2020-2024*). A nice example is the Healthy school initiative (*Gezonde school*) focusing on primary and secondary schools. The number of schools participating in this initiative is increasing, but still only 8% of the primary schools and 17% of the secondary schools.[114, 115] The Dutch Health council (*Gezondheidsraad*) provided physical activity guidelines for children in accordance with the World Health Organization, but these are only general advices and responsible stakeholders are lacking.[116] A downside of such advices is that they are more often picked up by schools in higher socioeconomic areas and parents from higher socioeconomic position, therefore creating an even wider socioeconomic inequality in health.[117] Providing stricter rules regarding outdoor play for all schools may help to increase outdoor play in all children, from the more wealthy to socioeconomic disadvantaged families. Regarding kindergartens, the focus of activities should shift from being mostly indoors to being mostly outdoors. For example in Norway, pre-school children are 70% of the day outdoors during summer, and 30% during wintertime, given that there is a nice and

safe outdoor play area.[118, 119] The low myopia prevalence in most Scandinavian countries is therefore not surprising.[120, 121] School interventions seem to be most promising, since all children, including those from socioeconomic disadvantaged families, need to participate.[122]

(Youth) Health care

Finally, lifestyle advice should be implemented in the consultation of healthcare professionals. The Dutch myopia treatment guideline advices more than 15 hours per week of outdoor exposure during daylight and no more than 20 minutes of continuous near work. A practical advice is the 20-20-2 rule; take a break of 20 seconds after 20 minutes of near work, and play outdoors for 2 hours a day.[88] Monitoring of lifestyle changes by continued contact with health professionals is necessary to maintain the new lifestyle.[92] As myopic children go regularly to the ophthalmologist, orthoptist or optometrist, these professionals need to keep encouraging outdoor play. However, eye care specialists will usually be in contact with children once they are already myopic. Lifestyle advice is preferably provided before myopia development has started, which shows an opportunity regarding youth healthcare vision screening policies. For example, a 5 year old emmetropic child without pathology will pass the youth healthcare vision screening, but will very likely develop myopia by the age of 6 or 7 and is therefore at high risk of ocular morbidities later in life.[6, 9] Implementing refractive error or axial length measurements in the screening process will identify this child before myopia has developed. Lifestyle advice could be provided to the parents of this particular child to postpone the age of onset. Furthermore, outdoor play has been associated not only with myopia, but also with sleeping problems,[123, 124] overweight or obesity,[125, 126] and psychosocial problems.[37, 127] Encouraging outdoor play during the regular youth healthcare visits of all Dutch children and their parents will also improve the health of children in a general way.

Methodological considerations

Measurement error

The lifestyle factors used in this thesis were mainly derived from questionnaires which were filled out by one of the parents of the child. Agreements between children's answers, objectively measured light levels and parents' answers in visual activities of their child were poor to fair.[128, 129] Random, or non-differential, measurement errors in the exposure, such as over-reporting or under-reporting outdoor exposure and near work, may bias the effect size towards the null.[130] This may have diluted the effect sizes in Chapters 6, 9 and 11 in which computer use, near work and outdoor exposure in relation to refractive error was investigated. Random measurement errors in mediating variables may result in a positively or negatively biased direct association between the exposure and the outcome.[131] In Chapters 4 and 8, differences in refractive error between gender, ethnic background and socioeconomic factors were only moderately explained by lifestyle variables, possibly due to measurement error in

the mediating variables. Regarding refractive error, the use of cycloplegic refraction is the golden standard in myopia research among children.[132] Cycloplegic refraction was introduced during the Generation R research phase at 9 years and continued in the research phase at 13 years. Analyses in Generation R data with spherical equivalent as outcome were therefore only performed in these children. In ALSPAC, noncycloplegic autorefraction was performed in all children during several research phases and cycloplegic refraction was additionally performed in a small subsample at 7 and 15 years. A comparison between spherical equivalent calculated by noncycloplegic and cycloplegic measurements showed a relatively good agreement, but was on average more negative in the noncycloplegic measurements.[133, 134] The noncycloplegic data from ALSPAC was therefore less sufficient to determine myopia prevalence, but sufficient to determine associations with spherical equivalent. In Generation R research phase at 6 years, the first part of the research phase at 9 years and in the RAMSES study, cycloplegic refraction was performed only in children with reduced visual acuity (>0.1 LogMAR or <0.8 decimal) in at least one eye or in children with an ophthalmic history. Those with visual acuity of 0.1 LogMAR or less, no glasses, and no ophthalmic history were classified as non-myopic based on previous studies.[135, 136] In the unlikely event that children with mild myopia still had a visual acuity of ≤0.1 LogMAR in both eyes, this may have led to an underrepresentation of myopia prevalence. Measurement error becomes problematic when the error is differential, thus related to the exposure or the outcome under study. It may lead to invalid results with either upwards or downwards biased effect sizes.[130] Within the population-based studies that were used in this thesis, measurement error was likely non-differential as the participants were unaware of the outcome under study and the exposure was often measured before the outcome.

Call for objective lifestyle data

Better options than questionnaires to obtain lifestyle data may be experience sampling methods or diaries, but both are time consuming, and children must be old enough to be able to work with these methods.[137, 138] The Myopia app, as described in Chapter 7, seems to be a promising tool in objectively measuring smartphone use and face to screen distance. It does, however, not objectively measure other types of near work and outdoor exposure. Several other objective measurements of near work and outdoor exposure have recently been developed. The Clouclip and Rangelife devices are worn on the right arm of the eyeglass frame and they register real-time working distances and ambient light illuminance levels.[139-141] Both devices are unfortunately only applicable to children with glasses or willing to wear glasses with plano lenses during the study period. FitSight fitness tracker and Actiwatch are smartwatches that record real-time ambient light illuminance levels and are connected to an application for iOS and Android smartphones.[142, 143] As it is possible to provide feedback on the time spent outdoors via the app, these applications may as well be used in interventional

studies. However, they may be challenging to use in colder climates when children wear long sleeved jackets that may cover the watch. The disadvantages of these newly developed devices still need to be processed, but they seem very promising for future myopia research.

Concluding thoughts

Myopia is a common disorder that may lead to ocular complications and visual impairment later in life. Children with increased risk to develop myopia in childhood and adolescence are those with a less hyperopic refractive error in early childhood. Lifestyle interventions - limiting near work and increasing outdoor play - are warranted at an early age and especially for those with myopic parents, non-Dutch background, from socioeconomic disadvantaged families and girls. Contributions from parents, schools, childcares, health care professionals as well as local and national authorities are needed to prevent children from myopia.

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Appendices

SUMMARY

Part I: Introduction

Chapter 1 gives a general introduction and describes the aims of the thesis. Myopia is a refractive error of the eye in which the focal plane falls in front of the retina because the axial length is too long. Glasses or contacts with concave lenses are needed to correct myopia and achieve sharp vision. Myopia development occurs in childhood or adolescence. The prevalence of myopia is increasing all around the world, which is problematic because in particular higher degrees of myopia are associated with retinal problems in adulthood which may cause visual impairment or even blindness.

The aims of this thesis were:

1. To determine the risk of pathologic consequences of low, moderate and high myopia.
2. To explore the prevalence of spectacle wear, refractive errors and myopia from early childhood to adulthood.
3. To investigate the association between screen time, outdoor exposure, and myopia.
4. To examine the relation between genetic and environmental risk factors and myopia.
5. To explain the social relevance of myopia for The Netherlands.

Part II: Consequences of myopia

In **Chapter 2**, we assessed the risk between degree of myopia, related pathological consequences, and blindness by performing a systematic literature search and meta-analyses. Low, moderate, and high myopia were all associated with increased risks of myopic macular degeneration, retinal detachment, posterior subcapsular cataract, nuclear cataract and open angle glaucoma. Visual impairment was strongly related to longer axial length, higher myopia degree and age over 60 years. Although high myopia carries the highest risk of complications and visual impairment, low and moderate myopia also have considerable risks.

Part III: Myopia prevalence from early childhood to adulthood

The prevalence of spectacle wear in (pre-)school children, and the share of myopia was investigated in **Chapter 3**. The prevalence of spectacle wear was 1.5%, 2.3%, 6.6%, 8.2% and 11.8% at 36, 45, 60, 72 and 84 months, respectively. Among children with spectacle wear at 72 months and 84 months, 29.8% and 34.6% already had myopia, respectively. This illustrates the urgency to implement myopia prevention strategies.

In **Chapter 4**, we explored gender differences in myopia development in children and adults. Female gender was associated with a negative spherical equivalent and myopia in the children,

but was inversely associated in the adults. Mediators of the association between gender and spherical equivalent in children were reading time and number of books read per month. Education was the most important mediator of the association in adults. Myopia shifted from girls in the young generation, to men in the older generation, which is likely attributed by lifestyle and education.

Chapter 5 is an editorial about quarantine myopia in schoolchildren during the COVID-19 pandemic in China. At age 13 years, more than 80% already had myopia, while the prevalence at this age in European children is 25%. Most compelling were the data in 6-year-old children. The prevalence of myopia jumped from 3.5% to 5.7% in 2015 to 2019 to 21.5%, an almost 400% increase, in 2020. For 7-year-old and 8 year-old children, this increase was respectively 200% and 40%. At older ages, the 2020 surplus was not apparent, but at these ages, the total myopia prevalence was already substantial in the years prior to 2020.

Part IV: Lifestyle factors and myopia development

In **Chapter 6**, we investigated the association between computer use at ages 3, 6 and 9 years, and myopia and axial elongation. Mean computer use was associated with myopia at age 9 and axial elongation between age 6 and 9, as was reading time and reading distance. The combined effect of near work (computer use, reading time and reading distance) showed an increased, while outdoor exposure showed a decreased odd ratio and the interaction term was significant. Within our sample of children, increased computer use was associated with myopia development. The effect of combined near work was decreased by outdoor exposure.

As near work, and in particular smartphone use is difficult to assess by questionnaire, we developed an app to investigate the association between smartphone and refractive error in **Chapter 7**. During schooldays, smartphone use was on average 3.71 hours/day, and was only borderline significantly associated with axial length corneal radius ratio and not with spherical equivalent. Continuous use was on average 6.42 episodes of 20 minutes use without breaks/day, and was significantly associated with spherical equivalent and axial length corneal radius ratio. This suggests that frequent breaks should become a recommendation for smartphone use in teenagers.

In **Chapter 8**, the aims were to evaluate socioeconomic inequalities in myopia incidence, eye growth, outdoor exposure and computer use, and to investigate if newly introduced physical activity spaces can reduce eye growth in school-aged children. Myopia incidence was higher in children with non-Dutch background, families with lower household income and lower maternal education. Children living <600 meters of a physical activity space did not have increased outdoor exposure, except those from families with lower maternal education. Newly introduced physical activity spaces were not associated with reduction of eye growth.

Part V: Lifestyle influence on genetic drivers

In Chapter 9, we investigated whether environmental risk factors can influence the genetic effect in children developing myopia. A genetic risk score and an environmental risk score were calculated and both were significantly associated with myopia and axial length corneal radius ratio, as was gene-environment interaction. The discriminative value of parental myopia was 0.67 similar to the values of the genetic and environmental risk score and improved to 0.73 by adding gene-environment interaction.

We examined whether risk factor effect sizes vary depending on children's position in the refractive error distribution using conditional quantile regression in **Chapter 10**. Effects associated with all risk factors (genetic risk; parental myopia; high time spent reading; low time outdoors) were larger for children in the extremes of the refractive error distribution than for emmetropes and low ametropes in the center of the distribution. This provides indirect evidence that emmetropization buffers against both genetic and environmental risk factors.

Part VI: Social relevance for the Netherlands

In **Chapter 11,** we provided the current state of myopia research and in practice. The prevalence of myopia is increasing: Currently almost 50% of the young Europen adults is myopic. In particular high myopia is associated with visual impairment or even blindness at a later age. Myopia is caused by a combination of genetic and environmental factors, such as increased near work and lack of outdoor exposure. The 20-20-2 rule is a practical advice to prevent myopia: After 20 minutes of near work, look into the distance for 20 seconds and go outside for 2 hours/day. In particular children with progressive myopia up to 12 years may benefit from treatment. Additional genetic testing should be considered when the degree of myopia is higher than the child's age.

Outdoor play makes children healthier! **Chapter 12** describes that an active lifestyle is particularly important for optimal growth and development of children. Restrictions due to the COVID-19 virus make this more visible. The professional network 'View Outside' collected the lifestyle consequences for visual, motoric, postural, weight, sleep and psychosocial youth health. We strongly recommend spending two hours a day outdoors. Other lifestyle measures are reducing sedentary behavior, rules on screen use and regular change of activities involving sitting.

Part VII: General discussion and appendices

Chapter 13 provides an interpretation of the main findings of this thesis, its implications and directions for future research.

SAMENVATTING

Deel I: Inleiding

Hoofdstuk 1 geeft een algemene inleiding en beschrijft het doel van het proefschrift. Myopie is een refractie afwijking waarbij het brandpunt vóór het netvlies valt omdat het oog te lang is. Een bril of contactlenzen met concave glazen zijn nodig om myopie te corrigeren en scherp te kunnen zien. Myopie ontwikkelt zich in de kindertijd of adolescentie. De prevalentie van myopie is wereldwijd aan het toenemen, dat is problematisch want met name hogere gradaties van myopie zijn geassocieerd met netvlies problemen op latere leeftijd waardoor slechtziendheid of zelfs blindheid kan ontstaan.

De doelstellingen van dit proefschrift waren:

1. Het bepalen van het risico op pathologische gevolgen van lage, matige en hoge myopie.
2. Het bestuderen van de prevalentie van brildragerschap, refractieafwijkingen en myopie van de vroege kinderjaren tot volwassenheid.
3. Het onderzoeken van de associatie tussen schermtijd, blootstelling aan daglicht en myopie.
4. Het bestuderen van de relatie tussen genetische en omgevingsrisicofactoren en myopie.
5. Het toelichten van de maatschappelijke relevantie van myopie voor Nederland.

Deel II: Gevolgen van myopie

In **Hoofdstuk 2** hebben we het risico tussen myopie, gerelateerde pathologische gevolgen en blindheid onderzocht door middel van een systematisch literatuuronderzoek en meta-analyses. Lage, matige en hoge myopie waren allemaal geassocieerd met een verhoogd risico op myope maculadegeneratie, netvliesloslatingen, posterieur subcapsulair cataract, nucleair cataract en openkamerhoekglaucoom. Slechtziendheid was sterk gerelateerd aan een langere axiale lengte, hogere mate van myopie en leeftijd boven de 60 jaar. Hoewel hoge myopie het grootste risico op complicaties en visuele beperkingen met zich meebrengt, hebben lage en matige myopie ook aanzienlijke risico's.

Deel III: Prevalentie van myopie van de vroege kinderjaren tot volwassenheid

De prevalentie van brildragerschap bij jonge kinderen, en het myopie aandeel daarvan werd onderzocht in **Hoofdstuk 3**. De prevalentie brildragerschap was 1,5%, 2,3%, 6,6%, 8,2% en 11,8% op respectievelijk 36, 45, 60, 72 en 84 maanden. Van de kinderen met bril op 72 maanden en 84 maanden had 29,8% en 34,6% al myopie. Dit illustreert de urgentie om myopie preventie maatregelen te implementeren.

In **Hoofdstuk 4** werden de verschillen tussen jongens en meisjes in myopie ontwikkeling onderzocht bij kinderen en volwassenen. Meisjes hadden een negatievere sferisch equivalent en meer myopie dan jongens onder de kinderen, maar deze associatie was omgekeerd bij de volwassenen. Mediatoren van de associatie tussen geslacht en sferisch equivalent bij kinderen waren leestijd en het aantal gelezen boeken per maand. Educatie was de belangrijkste mediator van de associatie bij volwassenen. Myopie kwam meer voor bij meisjes in de jongere generatie en mannen in de oudere generatie, waarschijnlijk door levensstijl en educatie.

Hoofdstuk 5 gaat over quarantaine-myopie bij schoolkinderen tijdens de COVID-19-pandemie in China. Meer dan 80% van de 13 jarige kinderen had in de voorgaande jaren al myopie, in vergelijking met 25% bij Europese kinderen op deze leeftijd. De grootste verandering voor en na de COVID-19 maatregelen was te zien in de 6-jarige kinderen. De prevalentie van myopie steeg van 3,5% naar 5,7% van 2015 tot 2019 naar 21,5%, een stijging van bijna 400%, in 2020. Bij de 7-jarige en 8-jarige kinderen was deze stijging respectievelijk 200% en 40%. Bij de oudere kinderen was geen duidelijke stijging te zien in 2020, maar de myopie prevalentie was al substantieel in de jaren voorafgaand aan 2020 bij deze leeftijdsgroepen.

Deel IV: Leefstijlfactoren en ontwikkeling van myopie

In **Hoofdstuk 6** hebben we de associatie tussen computergebruik op de leeftijd van 3, 6 en 9 jaar, en myopie en axiale groei onderzocht. Computergebruik was geassocieerd met myopie op 9-jarige leeftijd en axiale groei tussen 6 en 9 jaar, evenals de leestijd en leesafstand. Het gecombineerde effect van dichtbij werk (computergebruik, leestijd en leesafstand) toonde een verhoogde odds ratio, terwijl blootstelling aan de buitenlucht een verlaagde odds ratio liet zien en de interactieterm was significant. Uit deze resultaten blijkt dat computergebruik is geassocieerd met myopie ontwikkeling bij deze kinderen. Het effect van gecombineerd dichtbij werk werd verminderd door blootstelling aan de buitenlucht.

Omdat dichtbij werk, en met name smartphonegebruik, moeilijk te meten is met een vragenlijst, hebben we voor **Hoofdstuk 7** een app ontwikkeld om het verband tussen smartphonegebruik en refractieafwijkingen te onderzoeken. Tijdens schooldagen was smartphonegebruik gemiddeld 3,71 uur/dag en dit was net niet significant geassocieerd met de axiale lengte cornea radius ratio en het sferisch equivalent. Continu smartphonegebruik was gemiddeld 6,42 episodes van 20 minuten zonder pauzes/dag, en was significant geassocieerd met het sferisch equivalent en de axiale lengte cornea radius ratio. Dit suggereert dat regelmatige pauzes in smartphone gebruik bij tieners aanbevolen moeten worden.

In **Hoofdstuk 8** onderzochten we de sociaaleconomische verschillen in myopie incidentie, ooggroei, buiten spelen en computergebruik, en bestudeerden we of speelveldjes in de buurt de ooggroei van schoolkinderen kunnen verminderen. Myopie incidentie was hoger

bij kinderen met een niet-Nederlandse achtergrond, uit gezinnen met een lager inkomen en met een lager educatie niveau van de moeder. Kinderen die <600 meter van een speelveldje woonden, kwamen niet meer buiten de rest, behalve de kinderen uit gezinnen met een lager opleidingsniveau van de moeder. Nieuw geïntroduceerde speelveldjes waren niet geassocieerd met een verminderde ooggroei.

Deel V: Leefstijlinvloed op genetische factoren

In **Hoofdstuk 9** hebben we onderzocht of omgevingsrisicofactoren het genetische effect op myopie ontwikkeling kunnen beïnvloeden. Een genetische risicoscore en een omgeving risicoscore werden berekend en beiden waren significant geassocieerd met myopie en axiale lengte cornea radius ratio, evenals de gen-omgevingsinteractie. De discriminerende waarde van myopie bij de ouders was 0,67, vergelijkbaar met die van de genetische en omgeving risicoscores, en nam toe tot 0,73 door het toevoegen van de gen-omgevingsinteractie.

We onderzochten of de effectgroottes van risicofactoren bij kinderen afhankelijk zijn van de positie op de refractieverdeling met behulp van conditionele kwantielregressie in **Hoofdstuk 10**. De effecten van alle risicofactoren (genetisch risico; ouderlijke myopie; veel tijd besteed aan lezen; weinig tijd buitenshuis) waren groter voor kinderen in de extremen van de refractieverdeling dan voor emmetropen en lage ametropen in het midden van de verdeling. Dit levert indirect bewijs op dat emmetropizatie tegen zowel genetische als omgevingsrisicofactoren kan bufferen.

Deel VI: Maatschappelijke relevantie voor Nederland

In **Hoofdstuk 11** geven we de huidige situatie omtrent myopie onderzoek en in de praktijk weer. Myopie komt steeds vaker voor: Momenteel is bijna 50% van alle jongvolwassenen in Europa myoop. Vooral hoge myopie is geassocieerd met slechtziendheid of zelfs blindheid op latere leeftijd. Het ontstaat door een combinatie van genetische en omgevingsfactoren, zoals het doen van veel dichtbijwerk en weinig buiten spelen. De door ons gelanceerde 20-20-2-regel is een praktisch advies om myopie te voorkomen: Kijk na 20 minuten dichtbijwerk 20 seconden in de verte en ga 2 uur per dag naar buiten. Vooral kinderen tot en met 12 jaar met progressieve myopie komen in aanmerking voor behandeling. Aanvullend erfelijkheidsonderzoek moet worden overwogen als de mate van myopie hoger is dan de leeftijd.

Meer buiten spelen maakt kinderen gezonder! In **Hoofdstuk 12** wordt beschreven dat een actieve leefstijl van groot belang is voor een optimale groei en ontwikkeling van kinderen. De beperkingen als gevolg van het COVID-19 virus maken dit extra zichtbaar. Het professionele netwerk 'Zicht op Buiten' bracht de gevolgen van te weinig beweging en buiten zijn voor de gezondheid van kinderen en jongeren in kaart, op het gebied van visus, motoriek, houding, overgewicht, slaap en psychosociale gezondheid. We bevelen sterk aan om twee uur per dag

naar buiten te gaan voor gezonde kinderogen. Andere leefstijl maatregelen zijn het verminderen van sedentair gedrag en regels over schermgebruik evenals regelmatig afwisselen van zittende activiteiten.

Deel VII: Algemene discussie en bijlages

Hoofdstuk 13 geeft een interpretatie van de hoofdbevindingen van dit proefschrift, de implicaties en richting voor vervolgonderzoek weer.

LIST OF PUBLICATIONS

Publications on which this thesis is based

Annechien E.G Haarman*, **Clair A. Enthoven***, J. Willem L. Tideman, Milly S. Tedja, Virginie J.M. Verhoeven, Caroline C.W. Klaver. The complications of myopia: a review and meta-analysis. *Investigative ophthalmology & visual science*, 2020, 61(4), 49-49.
* authors contributed equally

Caroline C.W. Klaver, Jan Roelof Polling, **Clair A. Enthoven**. 2020 As the year of quarantine myopia. *JAMA ophthalmology*, 2021, 139(3), 300-301.

Clair A. Enthoven, J. Willem L. Tideman, Jan Roelof Polling, Junwen Yang-Huang, Hein Raat, Caroline C.W. Klaver. The impact of computer use on myopia development in childhood: the Generation R study. *Preventive medicine*, 2020, 132, 105988.

Clair A. Enthoven, J. Willem L., Tideman, Jan Roelof Polling, Milly S. Tedja, Hein Raat, Adriana I. Iglesias, Virginie J.M. Verhoeven, Caroline C.W. Klaver Interaction between lifestyle and genetic susceptibility in myopia: the Generation R study. *European journal of epidemiology*, 2019, 34(8), 777-784.

Alfred Pozarickij*, **Clair A. Enthoven***, Neema Ghorbani Mojarrad, Denis Plotnikov, Milly S. Tedja, Annechien E.G Haarman, J. Willem L. Tideman, Jan Roelof Polling, Kate Northstone, Cathy Williams, Caroline C. W. Klaver, Jeremy A. Guggenheim. Evidence that emmetropization buffers against both genetic and environmental risk factors for myopia. *Investigative ophthalmology & visual science,* 2020, 61(2), 41-41.
*authors contributed equally

Clair A. Enthoven, Jan Roelof Polling, Annechien E.G. Haarman, Virginie J.M. Verhoeven, Caroline C.W. Klaver & myopie groep Erasmus MC. Waarom dragen steeds meer kinderen een bril? *Praktische Pediatrie*, 2021, 15(1), 66-70.

Vasanthi. Iyer*, **Clair .A. Enthoven***, Caroline C.W. Klaver, Edith H. Mulder, André Soeterbroek & leden 'Zicht op Buiten'. Natuurlijk naar buiten! *Accepted in TSG.*
*authors contributed equally

Vasanthi Iyer*, **Clair A. Enthoven***, Paula van Dommelen, Ashwin van Samkar, Johanna H. Groenewoud, Vincent W.V. Jaddoe, Sijmen A. Reijneveld, Caroline C.W. Klaver. Rates of spectacle wear and associated myopia in early childhood. *Submitted.*
*authors contributed equally

Clair A. Enthoven, Jan Roelof Polling, Timo Verzijden, J. Willem L. Tideman, Nora Al-Jaffar, Pauline W. Jansen, Hein Raat, Lauwerens Metz, Virginie J.M. Verhoeven, Caroline C.W. Klaver. Smartphone use associated with refractive error in teenagers; the Myopia app Study. *Accepted in Ophthalmology.*

Clair A. Enthoven, Famke J.M. Mölenberg, J. Willem L. Tideman, Jan Roelof Polling, Jeremy A. Labrecque, Hein Raat, Frank J. van Lenthe, Caroline C.W. Klaver. Physical activity spaces not effective against socioeconomic inequalities in myopia incidence. The Generation R study. *Accepted in Optometry and Vision Science.*

Clair A. Enthoven, Annechien E. G. Haarman, Joanna Swierkowska, J. Willem L. Tideman, Jan Roelof Polling, Hein Raat, Virginie J.M. Verhoeven, Caroline C. W. Klaver. Gender issues in myopia: a changing paradigm. *To be submitted.*

Not part of this thesis

Clair A. Enthoven and Caroline C. W. Klaver. Response to Dr. Watts letter on "The impact of computer use on myopia development in childhood". *Preventive Medicine*, 2020 139: 106069.

Annechien E.G. Haarman, **Clair .A. Enthoven**, Milly S. Tedja, Jan Roelof Polling, J. Willem .L. Tideman, Jan E.E. Keunen, Camiel J.F. Boon, Janine F. Felix, Hein Raat, Annette J.M. Geerards, Gré P.M. Luyten, Gwyneth A. van Rijn, Virginie J.M. Verhoeven, Caroline C.W. Klaver. Phenotypic consequences of the GJD2 Risk genotype in myopia development. *Investigative ophthalmology & visual science,* 2021.

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Eric. F Thee, Magda A. Meester-Smoor, Daniel T. Luttikhuizen, Johanna. M. Colijn, **Clair. A. Enthoven**, Annechien E. G. Haarman, Dimitris Rizopoulos, Caroline C. W. Klaver, for the EyeNED Reading Center. Performance of Classification Systems for Age-Related Macular Degeneration in the Rotterdam Study. *Translational vision science & technology,* 2020, 9(2): 26-26.

Inge Schalkers, **Clair A. Enthoven**, Joske F.G. Bunders, Christine W.M. Dedding. When to invest in clinical guidelines for children? A practice oriented tool to facilitate decision-making. *Journal of evaluation in clinical practice,* 2017, 23(1), 79-88.

Annechien E.G. Haarman, Milly S. Tedja, Corina Brussee, **Clair A. Enthoven**, Gwyneth A. van Rijn, Johannes R. Vingerling, Jan E.E. Keunen, Camiel J.F. Boon, Annette J.M. Geerards, Gré P.M. Luyten, Virginie J.M. Verhoeven, Caroline C.W. Klaver. The prevalence of retinal complications in highly myopic Europeans. *Submitted.*

Jan Roelof Polling, J. Willem L. Tideman, Marian C. Verkaik-Rijneveld, **Clair A. Enthoven**, Vincent W.V. Jaddoe, Johannes R. Vingerling, Caroline C.W. Klaver, Sjoukje E. Loudon. Ophthalmological findings in a Pediatric Population. *To be submitted.*

Adriana G. Roth, J. Willem L. Tideman, Jan Roelof Polling, **Clair A. Enthoven**, Bea Spek, Marian C. Verkaik-Rijneveld, Vincent W.V. Jaddoe, Caroline C.W. Klaver. Remaining hyperopic in this millennium: The Generation R study. *To be submitted.*

ABOUT THE AUTHOR

Clair Anna Enthoven was born on the 31st of July 1991 in Naaldwijk, The Netherlands. She graduated from secondary school ISW Tiendweg with a Nature and Health profile (Natuur en Gezondheid) in 2008. Thereafter she studied Optometry at the Utrecht University of Applied Sciences and obtained her bachelor's degree in 2012. She continued studying with a pre-master in Health Sciences which she obtained in 2013, followed by a two-year research master in Management, Policy Analysis and Entrepreneurship in Health and Life sciences with the specialization International Public Health at the VU University of Amsterdam. During her master program, she performed two research internships using both qualitative and quantitative research methods. The first project was about clinical guideline development for children at the Child and Hospital Foundation (Stichting Kind en Ziekenhuis) and the Athena Institute in 2014. The second project was about the accessibility to eye healthcare at the Brien Holden Vision Institute in Phnom Penh, Cambodia in 2015. She stayed in South-East Asia to travel and obtained her master's degree in 2016. In the same year, she started as a research assistant at the Department of Ophthalmology, Epidemiology and Generation R which resulted in a PhD program under supervision of Prof. dr. Caroline Klaver in 2017. Clair coordinated the ophthalmologic measurements and implemented a mobile application within the Generation R study. In addition, she conducted a study on smartphone use and refractive error using a mobile application among 300 high school children. Clair obtained the master's degree in Clinical Epidemiology at the Netherlands Institute of Health Sciences (NIHES) in 2019. As part of her PhD program, she presented her work at national and international conferences. Clair won the MIT Outstanding Poster Competition at the ARVO conference in 2021. In the same year, she started as a postdoctoral researcher at the Department of Psychology, Education and Child Studies, Erasmus University Rotterdam where she will pursue her scientific career.

PHD PORTFOLIO

Name PhD student:	Clair Enthoven
Erasmus MC department:	The Generation R Study, Ophthalmology & Epidemiology
Research school:	Netherlands Institute for Health Sciences (NIHES)
PhD period:	2017-2021
Promotor:	Prof. dr. C.C.W. Klaver
Copromotor:	dr. V.J.M Verhoeven

PhD training	Year	ECTS
MSc Health sciences, specialization Clinical Epidemiology		
Study Design	2016	4.3
Biostatistical methods I	2016	5.7
Biostatistical methods II	2016	4.3
Clinical Epidemiology	2017	3.7
Clinical Translation to Epidemiology	2017	2.0
Principles in Causal Inference	2018	1.4
Principles of Research in Medicine and Epidemiology	2016	0.7
Methods of Clinical Research	2016	0.7
Clinical Trials	2016	0.7
Health economics	2016	0.7
The Practice of Epidemiologic Analysis	2016	0.7
Fundamentals of Medical Decision Making	2016	0.7
Elective courses		
Repeated Measurements in Clinical Studies	2017	1.4
Missing Values in Clinical Research	2017	0.7
Topics in Meta-analysis	2017	0.7
Principles of Genetic Epidemiology	2017	0.7
Genomics in Molecular Medicine	2017	1.4
Joint Models for Longitudinal and Survival Data	2019	0.7
Courses for the Quantitative Researcher	2017	1.4
Genome Wide Association Studies	2017	0.7
Causal Inference	2018	1.4
Skills courses		
Scientific Integrity	2018	0.3

1 ECTS (European Credit Transfer System) is equal to a workload of 28 hours.

PhD training	Year	ECTS
Good Clinical Practice	2018	0.1
Radiation hygiene and protection level 5R	2016	0.7
MRI safety	2017	0.3
Systematic Literature Retrieval in Pubmed	2018	0.2
Basic Life Support adults and children	2018	0.2
Other courses		
SNPs and Human Diseases	2017	2.0
Seminars, symposia and workshops		
Youth Health Care refresher training, Groningen	2016	1.0
Growing up in a digital world (Youth Health care), Lunteren	2019	1.0
Current affairs program Youth Health care, Amsterdam	2021	1.0
Generation R Research meeting, Rotterdam	2017	0.5
Invited speaker at Conversas	2020	0.3
(Inter)national conferences		
Oral presentations		
Dutch Optometry Society conference, Den Bosch	2019	1.0
Dutch Optometry Society conference (digital)	2021	0.5
Dutch Orthoptic Society conference, Bunnik	2017	1.0
Myopia Management Conference, Apeldoorn	2017	1.0
Dutch Ophthalmology Society conference, Maastricht	2017	0.5
Dutch Ophthalmology Society conference, Groningen	2020	0.5
Poster presentations		
Health sciences day, Rotterdam	2019	0.5
Association for Research in Vision and Ophthalmology, Baltimore	2017	0.5
Association for Research in Vision and Ophthalmology, Honolulu	2018	0.5
Association for Research in Vision and Ophthalmology, Vancouver	2019	0.5
International Myopia Conference, Birmingham	2017	0.5
International Myopia Conference, Tokyo	2019	0.5
Dutch Ophthalmology PhD Students conference, Nijmegen	2018	0.5
Teaching activities		
Supervising students	2017-2021	5.0
Other teaching activities		
Guest teacher, University of Applied Sciences Utrecht	2017-2019	1.5
Teaching assistant Biostatistical methods I, NIHES	2019	0.3

1 ECTS (European Credit Transfer System) is equal to a workload of 28 hours.

PhD training	Year	ECTS
Teaching assistant Advances in Clinical Epidemiology, NIHES	2020	0.7
Other activities		
Generation R general tasks	2017-2018	50.0
Supervision and training of ophthalmologic data collection in Generation R	2016-2021	6.0
Reviewer for several international journals	2020-today	3.0
Organizing Dutch Ophthalmology PhD conference	2018-2019	2.0

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