Development and management of refractive error in childhood

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Voor mijn ouders

With all there is, why settle for just a piece of sky?

Alan & Marilyn Bergman

Contents

1.

General introduction

Parts of this chapter were obtained from the published paper:

Polling JR, Verhoeven VJ, Tideman JW, Klaver CC. Duke-Elder's Views on Prognosis, Prophylaxis, and Treatment of Myopia: Way Ahead of His Time. Strabismus 2016;24(1):40-3.

General introduction

This thesis comprises studies on the development and treatment of childhood refractive error and myopia in particular. In the introduction, I will focus on the insights of prevention of myopia from a historic perspective showing that the ideas we have today are not new. Then I explain therapies for progressive myopia, and subsequently discuss the structure of my thesis.

Myopia has become the fastest growing eye anomaly worldwide.[1] (figure 1) The trait develops in childhood, with a peak incidence between the ages of 12-14.[2] Myopia is one of the greatest new prevention and treatment goals envisaged in paediatric ophthalmology.[3] The need to solve this problem lies in the fact that severe myopia can lead to impaired vision in later life.[4] This is because the degree of axial length is directly associated with an increased risk of ocular complications that cause irreversible visual impairment.[5] The cause of myopia is complex.[6] More than 500 genetic factors that can contribute to the development of myopia have now been identified.[7] However, prevention of axial length elongation and therefore myopia must be mainly sought in lifestyle adjustments.[8] Several studies have shown that more time spent outdoor and less close work result in a delayed growth in axial length, so that the onset of the myopia is postponed or will no longer occur at all.[9]

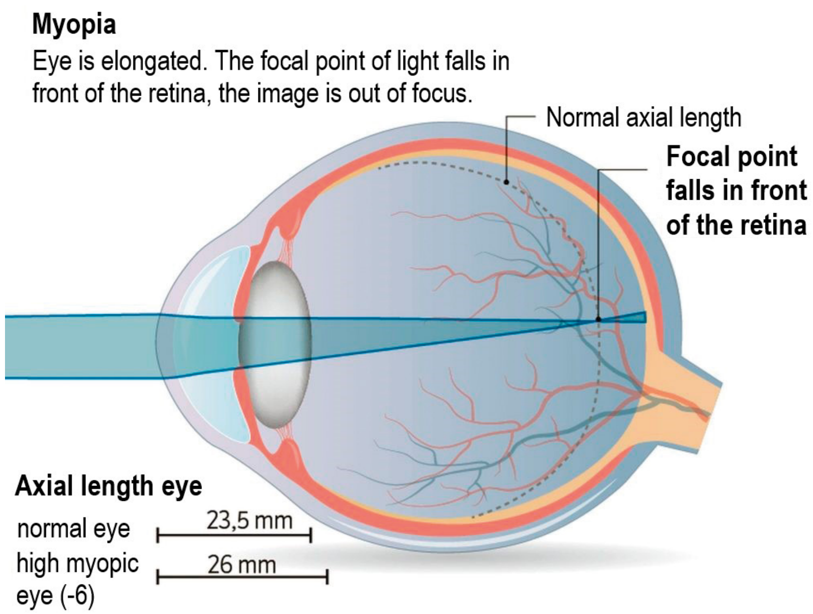

Figure 1: Elongation of the axial length in an eye with myopia

Historical perspective

Before epidemiologic studies had been conducted, Sir Stewart Duke-Elder (1898-1978) wrote in the second edition of The Practice of Refraction, published in 1935 a visionary piece of work on the prognosis, prophylaxis and treatment of myopia.[10] He addressed the risk factor age as an important risk factor for high myopia. When myopia onset develops in the first decade of life, high myopia in adulthood is usually seen.[11, 12] Mild myopia can develop in the teenage years or even in early adulthood.[13] High myopia, in particular, is associated with a significant risk of visual complications, such as myopic macular degeneration, glaucoma, and retinal detachment.[14-16] One in three high myopic persons will develop severe visual impairment in the course of life due to these complications.[17] The risk of severe visual impairment increases significantly with each diopter or axial length elongation. More than 90% of the eyes with an axial length more than 30 mm end in a visual acuity <0.3 (20/80).[16, 17]
Duke-Elder well recognized the influence of environmental factors on myopia. He suggested that cases with strong progressive myopia should abandon school and spend a complete holiday in the country for a year. This implies that he knew that the condition was related to both education and urban regions. Many recent studies have shown that lifestyle factors indeed play an important role in the onset and progression of this trait.[18, 19] In particular, education is a risk factor that is highly associated with myopia; individuals with a university or higher vocational education have a 5 to 8 times higher risk of myopia than those who have attended only primary school. Similar effects are observed for urban versus rural areas. Studies in Asia show an almost doubled prevalence and progression rate for urban regions.[20] Two explanations may underlie these observations: (1) Myopic children spend less time outdoors than non myopic children, and (2) they perform more near work at an earlier age.[21-23] The protection conveyed by being outdoors is thought to be determined by light intensity[24]; while illuminance indoors is about 500 lux, light levels outdoors are generally greater than 20,000 lux. Higher light intensity appears to cause dopamine release by the amacrine cells in the retina,[25] and there is now ample evidence that dopamine can slow down elongation of the eyeball.[26] The association with near work is less apparent. This factor has been difficult to study: use of handheld digital tablets and reading show inconsistency and low reproducibility between studies.[27, 28] A current hypothesis is that near work triggers myopia due to the long duration of hyperopic defocus in the peripheral retina,[29] particularly in eyes with a prelate shape.[30, 31]

Sir Duke-Elder suggested that adequate correction by glasses, an abundance of fresh air and exercise, intake of vitamin D and calcium to increase the calcium-phosphorus ratio, and restriction of near work and education can eliminate the progression of myopia. How well do these concepts resist the passage of time? Several studies investigated the correction of the partial and full cycloplegic correction of refractive error, and observed a substantially higher rate of progression (up to 25%) when myopes were deliberately under corrected by 0.75D.[32] Others found that increasing outdoor exposure rather than exercise per se was associated with less development of myopia and a more hyperopic refraction.[28] A randomized clinical trial in 1903 Chinese children showed that 40 minutes of extra outdoor exposure caused a statistically significant decrease in the newly detected myopes and a reduced myopic shift after a period of 3 years.[33] Vitamin D and calcium supplementation trials have not been carried out, but several studies point out a protective role for higher vitamin D serum levels.[34-36] Restricting reading or withholding a child from education would now face many ethical issues,[37] but a more balanced outdoor-indoor ratio is good advice to all parents and teachers, as well as policy makers in childhood education.

Most regimens that Sir Duke-Elder recommended addressed lifestyle issues. Currently, more active control of myopia progression is possible.[38, 39] Optical and pharmacological treatments have proven their effectiveness in large randomized trials, however, in order to guarantee effective implementation, large-scale real world studies are needed to prove the applicability of theinterventions.[40] Remarkably, Sir Duke-Elder did not refer to the earliest report of atropine treatment for myopia which had been published as early as 1868.[41-43]

Therapies for progressive myopia

Providers of child care should be aware of the fact that the growing eye is not directly at risk, but is vulnerable to permanent changes in adulthood. On the other hand, the fight against myopia should not stand in the way of well-known and preventable causes in paediatric ophthalmology such as amblyopia and refractive disorders other than myopia. Early detection and treatment of amblyopia remains essential for effective child care, and rapid recognition of refractive disorders, is just as important as strabismus and developmental disorders of the eye. Only recognition of all eye abnormalities will lead to an improved visual prognosis for the child.[44, 45]

The eye at birth starts relatively small with an axial length of 17 millimetres and a hyperopic refractive error. This grows towards the emmetropic state fast, especially in the first years of life, to an axial length of 20 millimetres.[46] After that, a normal eye slowly grows to 23.50 millimetres, but maintains the emmetropic state.[47] By the age of 20 most eyes are fully grown and the refractive state of the eye will change minimally.[48]

Unfortunately, population studies in young participants show that the final refraction is shifting more and more to a longer axial length with more myopic refraction.[49] Especially in urban Southeast Asian populations, the prevalence is increasing alarmingly to more than 80-90%. Europe appears to be following the trend, albeit to a lesser extent as ‘only’ half of all people in their twenties now have myopia.[3] As mentioned, it is precisely the myopia -6 dioptre or an axial length of 26 mm or more that is associated with ocular morbidity: 1 in 3 people with high myopia develop visual impairment due to structural changes of the retina (retina) and optic nerve, which can lead to myopic macular degeneration, retinal detachment, cataracts and glaucoma.[4] (figure 2)

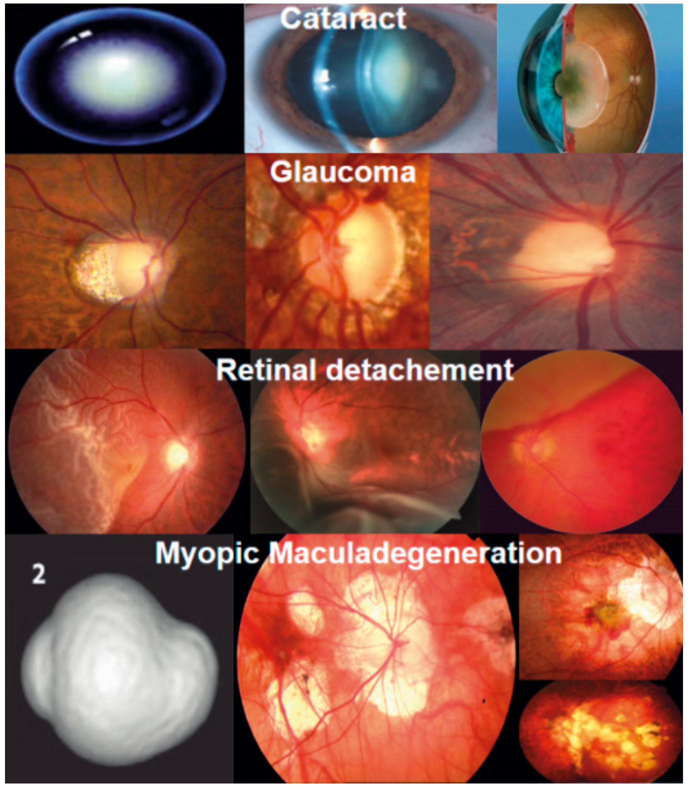

Figure 2: Examples of ocular complication due to high myopia

Intervention comes into play when the onset of myopia is early in life and lifestyle adjustments alone are no longer sufficient to inhibit myopia progression. Various interventions have been developed for these children in recent years and have proven to be effective. The main goal of the treatment of children with progressive myopia is to slow growth and preferably prevent high myopia.[50] Complete stopping of the growth of the eye is often not achieved by the current treatment options, but there is a large variation in efficacy.[51] It is clear that these treatments are effective in randomized clinical trials and these therapies are now offered by eye healthcare providers involved in myopia management. To what extent these therapies also work in the real world is still a question that needs to be answered. Most meta-analyses, white papers and views of national and international professional organizations in ophthalmology conclude that to date there are three potential therapies to slow the growth of the eye in progressive myopia.[52-54]:

1. *Atropine eye drops in different dosages to increase the dopamine level in the eye after instillation*

2. *Ortho-K contact lenses to temporarily reshape the cornea to change the focus on the peripheral retina*

3. *Soft bifocal or multifocal contact lenses based on the centre-distance principle to change the focus on peripheral retina.*

In the last year, the first publication of a potentially new effective therapy has been published. This is a type of spectacle lens that defocuses the peripheral retina.[55] Several studies on different types of peripheral defocus lenses will be released in the coming years and preliminary results show good effectiveness.[56]

Atropine

Atropine eye drops have been known to stabilize myopia for over 100 years.[41] Atropine is a non-selective muscarinic receptor antagonist available as an eye drop in various concentrations (1%, 0.5%, 0.25%, 0.1%, 0.05%, 0.01%). The presence of muscarinic receptors has been demonstrated in the retina and in the sclera, but the precise role they play in the growth of the eye is not yet clear.[57] However, atropine has recently been shown to increase dopamine levels in the retina, and dopamine has previously been found to inhibit eye growth.[58] Another effect of atropine is to increase NO, which is also a mediator of eye growth.[59] For a long time, people were reluctant to use atropine because of the pupil dilation which could result in phototoxicity, and because of accommodation paresis.[60] Phototoxic damage from high dose atropine was investigated using ERGs in the ATOM study and it was found that the amplitudes and latency times in myopes with and without treatment were equally reduced.[61] Permanent damage to the accommodation amplitude due to atropine use has also been investigated in ATOM. This study showed that 0.5% atropine after 1 year gives 0.44D less accommodation than 0.01% atropine, which is not clinically significant.[62] Allergic conjunctivitis to the allergens in atropine unfortunately occurs in ± 5% of users.[63]

The effectiveness of atropine has been demonstrated in several studies. As early as 1971, an American study reported administration of atropine 1% daily in 150 children with myopia. After one year, 75% showed no progression.[64] Since 1989 several randomized trials have been conducted in Asia, of which ATOM (Atropine in the Treatment of Myopia) from Singapore was the most important study.[65, 66] In this trial, 400 children were treated with different concentrations of atropine or with a placebo for two years. A clear dose-response relationship became evident. The decrease in spherical equivalent (SER) was significant for all concentrations, however, the decrease in axial length growth was significant only for atropine 0.5% and 1.0%; 0.01% showed similar growth of axial length as the placebo.[63] When treatment was discontinued after 2 years, a rebound effect of refractive error was observed, especially at the high doses (0.5% and 1.0%).[62] Thus, high dosages of atropine are very effective but apparently should not be discontinued abruptly. A tapering schedule could prevent this refractive error rebound effect.[67]

Low dose atropine (0.01% - 0.05%) has been in the spotlight for quite some time because of the low risk of side effects.[68] At this concentration, only 4% complain of photophobia and 2% have reading complaints. The pupil dilation is < 1.5 mm and the accommodation paresis is ~ 1D in both Asian and European populations.[69, 70] However, the efficacy of this concentration on axial length is limited: the ATOM study showed no reduction in axial length increase, the LAMP study a 12% reduction after 12 months.[71] Various trials are currently underway to test the efficacy of low dosages as a primary treatment.

Orthokeratology

Orthokeratology or Ortho-K is a temporary correction of myopia and astigmatism by using a specially shaped contact lens.[72] By wearing this contact lens at night, you can see clearly during the day without optical aids.[73] When wearing is discontinued, the cornea will return to its original shape after approximately 2 weeks. Initially, Ortho-K lenses were only intended to replace optical correction during the day, but they have now been proven to be effective in myopia control for the long run as well.[74] The underlying mechanism of action is change of the peripheral hyperopia into a myopic defocus, slowing axial growth.[75]

There are several studies on the efficacy of Ortho-K.[74] In 2005, the LORIC study compared the axis length of 35 children (7-12 years) who wore Ortho-K lenses for a year with a historical cohort of children who had monofocal glasses and found a 54% decrease in axial length progression in the Ortho K group (0.29 vs. 0.54 mm). Other clinical studies reported a reduction between 32-55%. A recent meta-analysis of several Ortho-K studies with a total of 435 children showed an average inhibition of axial length growth of -0.26 mm / year compared to the control groups, a reduction of 43%.[76]

There are drawbacks to using Ortho-K contact lenses. The most frequently reported complaints of ortho-K are defocus complaints; these can be solved by changing the lens fit so that the central part is in the visual axis. Corneal complications can also occur with or without loss of vision, the latter include, for example, a pigmented ring or an altered nerve pattern (fibrillary lines).[77, 78] The first includes central corneal staining that can lead to vision loss. In addition, microbial keratitis is the most notorious complication, with insufficient cleaning of the contact lens being the source of infection in most cases.[79, 80] These occur most commonly in early adolescence.[81]

Bifocal or Multifocal contact lenses

Soft multifocal contact lenses were initially designed for presbyopia, but are now increasingly used for myopia management.[82] Only the lenses with centre-distance, that is, centrally the refractive correction for distance, have been investigated in myopia studies.[83] These lenses can have a gradual increase of plus addition in the periphery (progressive design) or in different zones (concentric design). The aim is to have a correction in the fovea where the focal point falls on the retina, while in the peripheral retina the focal point falls in front of the retina (myopic defocus). This will reduce or remove the hyperopic defocus in the periphery that leads to myopia progression.[84]

Between 2011 and 2020, several randomized trials with soft multifocal (MF) contact lenses have been published. Studies used lenses with a concentric design and lenses with a progressive design. In 2 studies, the control group wore monofocal glasses; in the other, the control group received a monofocal soft contact lens.[51, 85] The refraction varied but averaged -2D (range -0.75 to -6.0) and ~ 75% of the children completed the study. The effectiveness of the MF lens in myopia management was quite consistent across the studies and the reduction in both refraction and axial length progression was between 29-52%. Although no complications were found, the dropout rate was greater in the contact lens group than in the spectacle group. The reasons for this were discomfort (11.7%) and problems with putting the lenses in and out (1.7%). The risks of keratitis is also increased, although somewhat less than ortho-K, except for the daily wear contact lenses.[85]

Hypothesis

Rapid progression of myopia has major implications for visual outcomes in adulthood. The primary hypothesis for this thesis is that modification of myopia during childhood and puberty by lifestyle and intervention can permanently influence the final degree of myopia at adulthood. Mapping the effects of early vision screening and gaining knowledge about the efficacy of the treatment of myopia progression is necessary to make the actions of modern eye care professionals relevant.

Aims of this thesis

The research questions that this thesis aims to answer are:

1. What are the eye problems occurring in early childhood? (chapter 2)
2. How does the eye grow and how does this effect myopic refractive error in adulthood? (chapter 3)
3. Can high dose atropine be applied for myopia control in the everyday clinic? (Chapter 4)
4. What can be recommended to general eye care practitioners with respect to management of myopia progression? (chapter 5)

GENERAL EPIDEMIOLOGICAL DESIGN

The study questions were investigated in various cohorts:

The Generation R Study

A population-based birth-cohort study of children who were born between April 2002 and January 2006 in Rotterdam, The Netherlands. As certainment of study participants started with women who were pregnant within this period. From the age of 5 years onwards, 9,276 children were invited to participate in the physical examination, including visual acuity and questionnaires about eye health, at the research center. The children had undergone population-based vision screening at the age of 6 and 12 months, and visual acuity testing at the age of 3 and 5 years before the visit. A total of 6690 children had participated in the physical examination at 6 years of age.

The Mieroszów eye project

A cohort a cross-sectional population-based study including children aged 2 months to 12 years from Mieroszów, a village located in the southwest of Poland. The children living in a rural area had not undergone a population-based vision screening. The village, has a population density of 7582 inhabitants. Six hundred twenty-eight children were identified by medical records from the only general practitioner in the village. All children were of Caucasian origin. The eye examination took place at the Mieroszówski Centrum Kultury in the center of Mieroszów. A complete medical history, visual acuity measurement and cycloplegic refraction was obtained.

The Drentse Refractive Error And Myopia (DREAM) Study population

The cohort comprised of subjects who bought their glasses from 1 of the 14 dispensing opticians from a chain of stores belonging to 1 family. The stores were located in the north of the Netherlands including the provinces Overijssel, Friesland, Groningen and Drenthe. The area has 1.7 million inhabitants and is classified as a non-urban area with 37% of the people living in an urban environment. Ethnicity was an unknown variable in this study; however, according to the open source Statistics Netherlands' database, persons in the region with a non-western background was approximately 3% in 1980 to 5% in 2015. Records of eyeglass orders were stored digitally since 1985, and all data gathered since that time up to 2015 entered the current analysis. Subjects were born between 1962 and 1997; follow-up time ranged from 1 to 22 years with a mean of 5.82 years (SD 4.1).

The Atropine 1 and 3 year follow-up Study

The design was a prospective clinic-based effectiveness study. The setting was a single centre study at the Erasmus Medical Centre in Rotterdam, the Netherlands, which included the Sophia Children's hospital. Erasmus Medical Centre has been a referral centre for myopia control since 2010. Inclusion criteria were consecutive children 5–16 years presenting with SER progression rate of at least 1D/year, or an SER of at least −2.5D in children 10 years and younger, or SER −5.0D in children aged 11 years or older. Exclusion criteria included those with paediatric pathology (e.g., amblyopia, strabismus, or systemic disorders) and low vision due to retinal dystrophies. The current reports included children who presented at our clinic between March 2011 and January 2015.

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2.0

Prevalence of amblyopia and refractive errors in an unscreened population of children

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Prevalence of amblyopia and refractive errors in an unscreened population of children

ABSTRACT

Purpose: To describe the frequency of refractive errors and amblyopia in unscreened children aged 2 months to 12 years of a rural town in Poland.

Methods: Five hundred ninety-one children were identified by medical records and examined in a standardized manner. Visual acuity was measured using LogMAR charts; refractive error was determined using retinoscopy or autorefraction after cycloplegia. Myopia was defined as spherical equivalent (SE) ≤ -0.50 D, emmetropia as SE between -0.5 D and +0.5 D, mild hyperopia as SE between +0.5 D and +2.0 D, and high hyperopia as SE ≥+2.0 D. Amblyopia was classified as best-corrected visual acuity ≥ 0.3 (≤ 20/40) LogMAR, in combination with a 2-LogMAR line difference between the two eyes and the presence of an amblyogenic factor.

Results: Refractive errors ranged from 84.2% in children aged up to 2 years to 75.5% in those aged 10-12 years. Refractive error showed a myopic shift with age; myopia prevalence increased from 2.2% in those aged 6 to 7 years to 6.3% in those aged 10 to 12 years. Of the examined children, 77 (16.3%) had refractive errors with visual loss; of these, 60 (78%) did use corrections. The prevalence of amblyopia was 3.1%, and refractive error attributed to the amblyopia in 9 of 13 (69%) children.

Conclusions: Refractive errors are common in Caucasian children and often remain undiagnosed. The prevalence of amblyopia was three times higher in this unscreened population compared with screened populations. Greater awareness of these common treatable visual conditions in children is warranted.

INTRODUCTION

Refractive errors and amblyopia are the most common causes of visual loss in children.[1-6] Frequencies, however, show large differences around the world.[7] Methods of detection vary widely, ethnicities differ, some countries have a screening program, and most countries use different methods for measurement of visual acuity.[7-12]

A number of studies report on prevalence of refractive error and myopia in children, andthey generally find differences in prevalence of myopia according to age and ethnicity.[12-16] Two studies in the United Kingdom including Caucasian children aged 6 to 7, and 12 to 13 years, respectively, found a myopia prevalence of 2.8 to 5.7% in the youngest, and 17.7 to 18.6% in the older age group.[4, 13, 17] South Asian children had significantly higher prevalence: 10.8% in those aged 6 to 7 years, and 36.8% in those aged 12 to 13 years. Ojaimi et al. also studied school children aged 5 to 8 years in Australia, and found an overall myopia prevalence of 1.4%. They found a significant difference between white European children (0.79%) and those belonging to other ethnicities (2.73%, p < 0.001).[17] Ip et al. studied the same Sydney Myopia Study children aged 11 to 14 and found an overall myopia prevalence of 11.9%. Large differences in prevalence were found between European Caucasian (4.6%) and East Asian (39.5%) children.[18] Other Asian studies found high myopia prevalence varying between 15 and 25% at the age of 10 years.[14]

There are some studies that investigated refractive error in Polish children. Czepita et al. studied myopia in rural children aged 10 to 14 years from the southeast part of Poland and found a myopia prevalence of 6.3% at the age 10 years increasing to a prevalence of 9.7% at the age of 12 years.[6] In another Polish study in semirural population of children aged 6 to 18 years, the prevalence of myopia was slightly higher: 11.3% in those aged 10 years to 14.4% in those aged 12 years.[6, 19] However these may be overestimates, as neither study used full cycloplegia to estimate refractive error.

Studies on the frequency of amblyopia have been carried out as well. Remarkable is the wide variation in criteria used for amblyopia.[20] Consensus criteria defined by a joint classification are: best-corrected visual acuity ≥0.3 (≤20/40) LogMAR in the affected eye, no underlying structural abnormality of the eye or visual pathway, a 2 LogMAR line difference between the two eyes and the presence of an amblyogenic factor.[21] A clinic based study among Polish immigrants in the United States using different criteria found an amblyopia percentage as high as 9%.[22] Studies using the consensus criteria generally found an amblyopia prevalence of ~2.5 to 3% in populations without a vision screening program, whereas a prevalence of 0.8 - 1.1% was found in populations with these programs.[2, 23] Apart from criteria, methodology of screening also varies widely between countries.[24-27] Some countries use visual acuity to screen for amblyopia, whereas others only screen for amblyogenic risk factors such as anisometropia.[26, 28-31] Most countries use their own visual acuity charts, which generally lack good internal and external reproducibility.[2, 20, 27] All these factors are known to distort prevalence estimates of amblyopia.[2] Vision screening alone detects amblyopia or refractive errors in need of correction but is not successful in detecting refractive errors per se.[32]

The aim of the current study was to determine the prevalence of refractive error and amblyopia in unscreened young Polish children of the same ethnicity. The examination included cycloplegic refraction in all children, and visual acuity testing in those old enough to be screened usingthe internationally accepted LogMAR chart. We used consensus criteria to define amblyopia, and explored its prevalence and causes.[10]

METHODS

Study Population

The Mieroszów eye project is a cross sectional population-based study including children aged 2 months to 12 years of the population of Mieroszów, a village located in the southwest of Poland. The village is rural, has a low population density (7582 inhabitants on 76 sq km of land), and has a lack of full medical health service.[33] Six hundred twenty-eight children were identified by medical records from the only general practitioner in the village. All children were of Caucasian origin.The research protocol adhered to the Declaration of Helsinki for research involving human subjects, and informed consent was obtained from all parents and guardians before the examination.

Eye Examination

The eye examination took place at the Mieroszowski Centrum Kultury in the center of Mieroszów. Acomplete medical history was obtained, with assistance of Polish medical students. Three trained ophthalmic nurses, three orthoptists, and one optometrist performed complete ophthalmological examination. Monocular visual acuity measurement was performed using LogMAR based charts at 3 m distance. Visual acuity was tested in all cooperative children aged ≥ 2 years. The type of chart depended on the age of the child: Lea Hyvärinen symbols were used for those aged 2 to 3 years, HOTV charts were used for those aged 4 to 6 years, and EDTRS letter charts for those aged ≥ 7 years. A linear visual acuity was used, and acuity was scored using the ETDRS Fast method.[34] To pass a line on the chart, three out of five symbols or letters needed to be answered correctly. Subjects who generally wore prescription glasses wore them during the test. Those who had ≥ 0.2 (≤ 20/32) LogMAR visual acuity were retested with trial glasses after refraction in a trial frame with their full spherical and cylindrical value. In children aged ≤ 2 years, visual acuity was scored based on the absence or presence of monocular fixation and pursuit movement. Stereo vision was examined using the Lang II test (Lang- Stereotest, Forch, Switzerland) according to the instructions in the information manual accompanying the test. Strabismus was tested using the cover test for near and distance fixation according to standard clinical procedures. Ocular movement was tested using a penlight for near. Refraction was measured after 30 to 45 min of cycloplegia with 1 drop of 1% cyclopentolate instilled in each eye. In children aged 2 to 12 years, refractive error was measured using a Nikon Retinomax 2 auto refractor (Nikon, Japan); in younger or uncooperative children, this was determined by retinoscopy using a Heine retinoscope (Heine Optotechnik, Herrsching, Germany) and lenses according to standard protocols. Ophthalmoscopy was performed using a Keeler binocular indirect ophthalmoscope by the optometrist.

Clinical Outcomes and Statistical Analysis

Main outcomes of the study were refractive error and amblyopia. Spherical equivalent (SE) was calculated as the sum of the full spherical value and half of the cylindrical value. We used the mean SE of both eyes in the analysis. Myopia was defined as SE ≤ -0.50 D; emmetropia as SE between -0.5 D and +0.5 D, mild hyperopia as SE between +0.5 D and +2.0 D; and high hyperopia as SE ≥ +2.0 D.[15, 35, 36] Analyses for amblyopia were performed in children who had reliable measurements of visual acuity (i.e., aged 3 years and older in this population). Amblyopia was defined as best-corrected visual acuity ≥ 0.3 (≤ 20/40) LogMAR in the affected eye, together with a 2 LogMAR line difference between the 2 eyes and the presence of an amblyogenic factor.[21, 27, 37] Amblyopia was categorized in three groups: (1) refractive amblyopia due to anisometropia of at least a 1.0 difference in SE refraction between the two eyes in the absence of strabismus, (2) strabismic amblyopia in the presence of a strabismus or a history of strabismus surgery without an isometropia or high refractive error or (3) a combination of strabismus and anisometropia.

All statistical analyses were performed using the PASW Statistics 17. Sample means and medians and their mean differences are reported with their range. Frequency differences between continuous and categorical variables were analyzed using Mann-Whitney test and Kruskal-Wallis test, and differences between continuous variables were analyzed using Spearman P. Linear regression was used to explore correlations.

RESULTS

Of the 628 eligible children, 591 children (94.1%) consented to examination at the research center. The median age was 7 years (range, 2 months to 12 years), and the gender distribution was equal (51% boys). The number of children and the refractive error defined in categories is presented per age group in Table 1.

Visual acuity increased significantly (Spearman $p = -0.316$, $p < 0.001$) with age, with a mean of 0.3 at 3 years to -0.04 at 12 years of age. (Fig. 1) The range of the SE was -5D to +7.75D with a median of +1D.The mean SE for boys was +1.1D (standard deviation, 1.1) and for girls +1.2D (standard deviation, 1.0; $p = 0.08$). SE showed a significant reduction with age ($p < 0.001$) from +2D at 2 months of age to +0.75D at 12 years of age, with the strongest decrease in hyperopia in the first year of life.

Table1.Distribution of refractive error in strata per age group (n, %)

Age	Total	Myopia	Emmetropia	Hyperopia	Significant Hyperopia
0	N = 20	0 (0%)	3 (15%)	10 (50%)	7 (35%)
1	N = 59	1 (1.7%)	5 (8.5%)	41 (69.5%)	12 (20.3%)
2	N = 46	1 (2.2%)	11 (23.9%)	26 (56.5%)	8 (17.4%)
3	N = 31	0 (0%)	4 (12.9%)	24 (77.4%)	3 (9.7%)
4	N = 26	0 (0%)	3 (11.5%)	22 (84.6%)	1 (3.8%)
5	N = 38	2 (5.3%)	5 (13.2%)	28 (73.7%)	3 (7.9%)
6	N = 45	2 (4.4%)	6 (13.3%)	29 (64.4%)	8 (17.8%)
7	N = 52	0 (0%)	11 (21.1%)	34 (65.4%)	7 (13.5%)
8	N = 45	0 (0%)	5 (11.1%)	32 (71.1%)	8 (17.8%)
9	N=72	5 (6.9%)	14 (19.4%)	48 (66.7%)	5 (6.9%)
10	N = 48	4 (8.3%)	14 (29.2%)	26 (54.2%)	4 (8.3%)
11	N = 47	4 (8.5%)	14 (29.8%)	25 (53.2%)	4 (8.5%)
12	N = 49	1 (2%)	10 (20.4%)	35 (71.4%)	3 (6.1%)

Spherical equivalent: myopia (≤-0.5 D), emmetropia (>-0.5 D to ≤+0.50 D), mild hyperopia (>+0.50 D to ≤+2.00 D), high hyperopia(>+2.00 D)

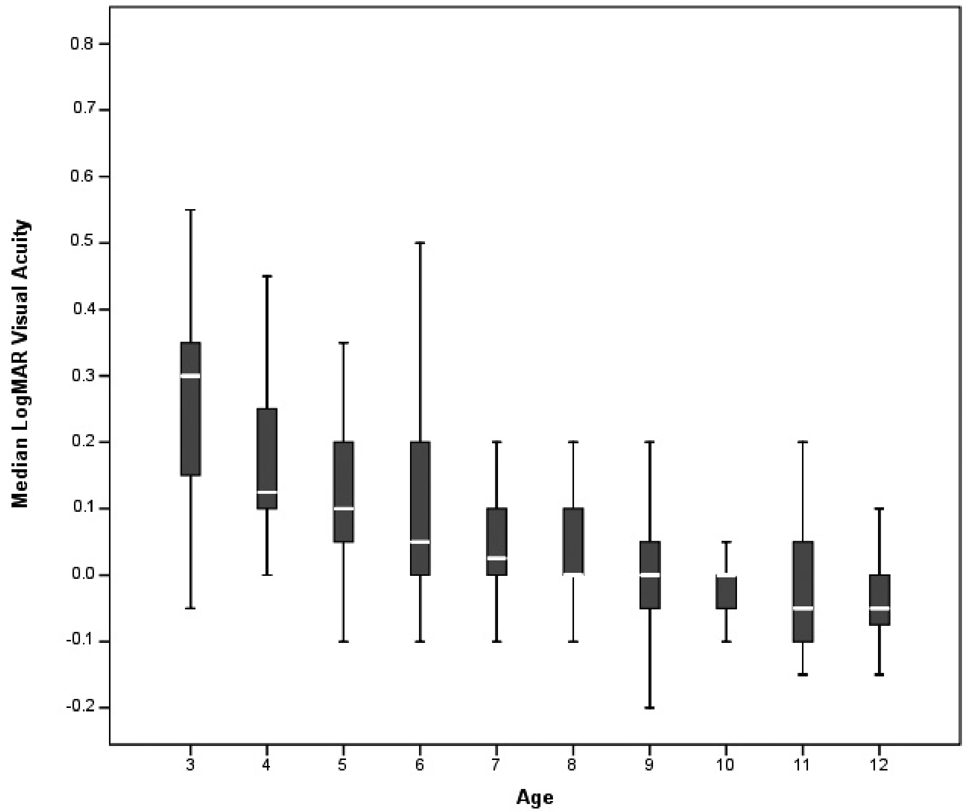

Figure 1: Visual acuity at presentation as a function of age (in years) in 421 Polish children of the Mieroszów eye project. The boundaries of the box depict the 25th and 75th percentile of the study population; the white band in the box is the median.

The distribution of refractive error by category for all the children is presented in Fig. 2. Of all children, 16.3% (n = 77 of 584) had decreased visual acuity; refractive error was the only cause. Of these 77 children, 13 (17%) had myopia (SE ≤ -0.5D), 2 (4%) had combined astigmatism with a mean emmetropic SE, 20 (26%) had mild hyperopia, and 42 (54%) had high hyperopia. Astigmatism < -0.5D or more was found in 58 children (9.8%); astigmatism < -1.25D was found in 19 children (3.2%). Astigmatism showed no relation with age (p = 0.53). Refractive error had not been corrected in 60 (78%) of the 77 children with decreased visual acuity, and wearing glasses did not appear to relate to refractive error (p = 0.72 for difference in SE between those with and those without glasses).

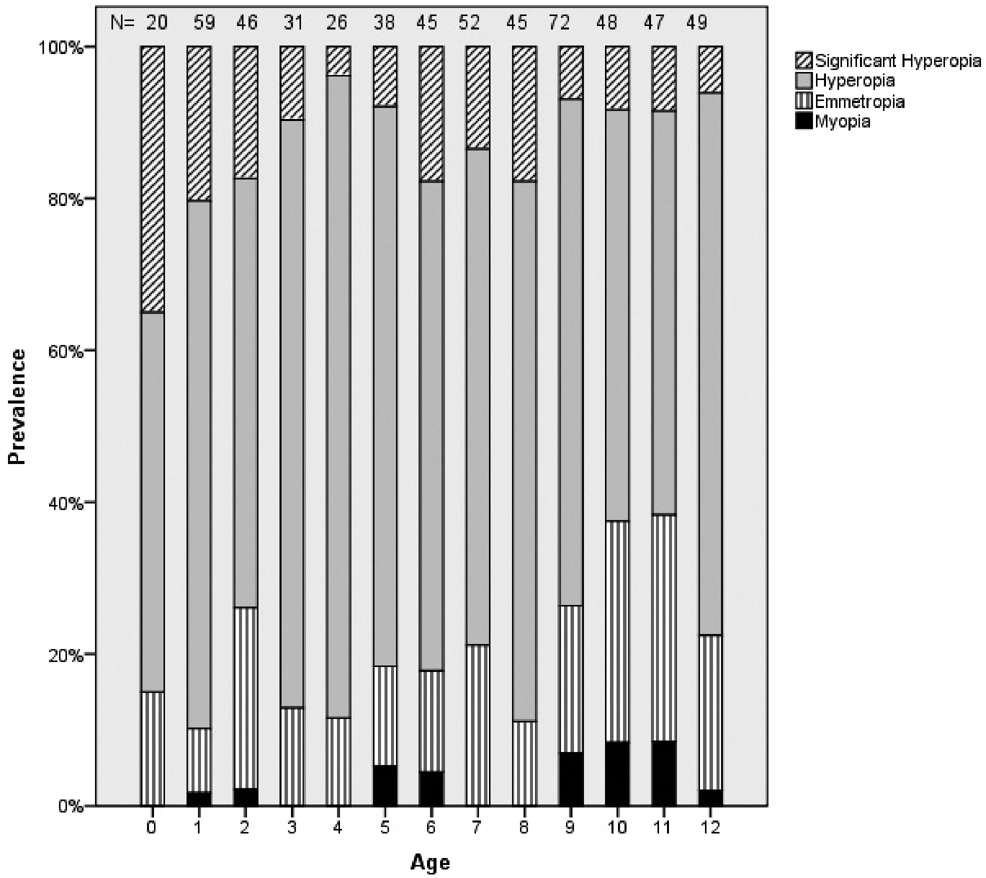

Figure 2: Distribution of refractive error in categories by age (in years) for 591 children from Mieroszów. Category spherical equivalent: myopia (≤ -0.5 D), emmetropia (> -0.5 D - ≤ +0.50 D), mild hyperopia (> +0.50 D - ≤ +2.00 D), high hyperopia (> +2.00 D)

LogMAR visual acuity could not be measured in 164 children (27%) because of young age or non-cooperation. However, all of these children had stable fixation and smooth pursuit. Visual acuity could be measured in 95% of children aged < 5 years. Of the 420 children with reliable measurements,13 (3.1%) had amblyopia according to our definition. The average age of the children with amblyopia was 6.9 (range 3 to 11) years; 11 children were older than 6 years. Amblyopia was caused by strabismus in three, anisometropia in 5, and combined mechanisms of anisometropia and strabismus in four children. Average visual acuity in the amblyopic eye due to amblyopia due to strabismus and combined mechanism was 0.6 (20/80) LogMAR; average visual acuity in those with amblyopia due to an isometropia was 0.4 (20/50) LogMAR. No ocular abnormalities such as retinopathy of the prematurity, cataracts, or other pathology were found.

DISCUSSION

This study in unscreened children living in a rural area of Poland shows that refractive errors are very common and shift toward myopia with age, amblyopia is higher in this unscreened population than in screened ones, and that uncorrected anisometropia is a prominent cause of amblyopia. Emmetropia occurred only in 12% of children < 2 years of age, and increased to 26% in children aged 10 to 12 years. Prevalence of significant hyperopia decreased from 28% in those < 2 years to 7% in those aged 10 to 12 years. The first occurrence of myopia was at the age of 1 year, and its prevalence increased from the age of 5 years onwards to 2.2% in 6 to 7 years and 6.3% in those aged 10 to 12 years. Comparison with earlier studies that had been performed in 10-year-old Polish children from another rural area shows highly comparable data (6.3% in 10 year-old and 9.7% in 12-year old children).[6] The prevalence of myopia, however, was considerably lower than that found in all Asian studies of young children, even in rural areas.[14, 15, 38, 39] Of all children, 16.3% (n =77) had decreased visual acuity due to refractive error, and only a small proportion of these had received correction. There was no difference in refractive error between those who wore glasses and those who did not. Economic reasons may have played a more important role herein than refractive errors per se.

The prevalence of amblyopia in these children was 3.1% (n =13), almost three times higher than in screened populations.[1, 2, 20, 37] The most important single cause of amblyopia was anisometropia.

There are strengths and limitations to this study. Strengths are the large age range with incorporation of very young children, the high participation rate, the comprehensive methods of visual acuity and refractive error measurements, and the identical ethnic background of all children. Among the limitations is the relatively low number of children in all age groups.

Normal development of refraction in children varies by genetics, environment and epoch.[10, 15, 16, 39, 40] Our study confirms the emmetropization process in the first decade, which is known to be strongest in the first 2 years of life.[41, 42] A distinct finding of this study is that the decline continues gradually in the years thereafter, with a slight mean hyperopia refractive error at the age of 12 years. For the population at large, visual acuity could be reliably measured from the age of 5 years onwards. The mean visual acuity in younger children was < 0.1 (20/25) LogMAR, but worse vision at a single examination in this age group does not necessarily indicate pathology. With our single test, visual acuity measurement was possible in 42% of the 3-year-old, 77% of the 4-year-old, and 95% of the 5-year-old children. More attempts for visual acuity testing would improve this fraction.

After uncorrected refractive error, amblyopia was the most important cause of decreased visual acuity in our study. The amblyopia prevalence of 3.1% was high when compared with that of screened populations.[2, 5] At present, there is no population-based screening program available in Poland. The degree of visual loss depended on the cause of amblyopia. Amblyopia with visual acuity > 0.4 (<20/50) LogMAR only corresponded with anisometropia, whereas amblyopia with visual acuity > 0.6 (< 20/60) LogMAR was only associated with strabismus.

What do our findings imply for screening programs in young children? Successful screening can reduce the prevalence of untreated amblyopia (LogMAR acuity > 20/50).[2] An important factor for success is screening for visual acuity, as screening for refractive error alone will not detect amblyopia caused by strabismus.[2, 27, 30] A beneficial side effect of visual acuity screening is the detection of only the refractive errors that are in need for correction, and not those that do not interfere with visual function.[10, 32]

CONCLUSIONS AND RECOMMENDATIONS

Refractive error sare common in very young children and show a myopic shift with age. The prevalence of amblyopia (3.1%) was relatively high in this unscreened Caucasian population. A national screening program including measurement of visual acuity may help reduce amblyopia prevalence. Improving awareness by education of parents, teachers, and health care providers may lead to reduction of uncorrected refractive errors.

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3.1

Axial length growth and the risk of developing myopia in European children

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Axial length growth and the risk of developing myopia in European children

ABSTRACT

Purpose: To generate percentile curves of axial length (AL) for European children, which can be used to estimate the risk of myopia in adulthood.

Methods: A total of 12,386 participants from the population-based studies Generation R (Dutch children measured at both 6 and 9 years of age; N = 6934), the Avon Longitudinal Study of Parents and Children (British children 15 years of age; N = 2495), and the Rotterdam Study III (Dutch adults 57 years of age; N = 2957) contributed to this study. AL and corneal curvature data were available for all participants; objective cycloplegic refractive error was available only for the Dutch participants. We calculated a percentile score for each Dutch child at 6 and 9 years of age.

Results: Mean (SD) AL was 22.36 (0.75) mm at 6 years, 23.10 (0.84) mm at 9 years, 23.41 (0.86) mm at 15 years, and 23.67 (1.26) at adulthood. AL differences after the age of 15 occurred only in the upper 50%, with the highest difference within the 95th percentile and above. A total of 354 children showed accelerated axial growth and increased by more than 10 percentiles from age 6 to 9 years; 162 of these children (45.8%) were myopic at 9 years of age, compared to 4.8% (85/1781) for the children whose AL did not increase by more than 10 percentiles.

Conclusions: This study provides normative values for AL that can be used to monitor eye growth in European children. These results can help clinicians detect excessive eye growth at an early age, thereby facilitating decision-making with respect to interventions for preventing and/or controlling myopia.

INTRODUCTION

Refractive errors such as myopia, hyperopia, and astigmatism are the most common ocular disorders worldwide. The prevalence of these conditions varies with both age and geographic location.[1-4] Myopia is most prevalent in Eastern Asia[5] and in the Western world[6, 7], whereas hyperopia is more prevalent in developing countries.[1]

Refractive error is the result of a mismatch between the various optical components of the eye, the most important of which are the cornea, the crystalline lens, and the eye's axial length (AL). In the first few years of age, the cornea's refractive power is reduced; the lens also loses refractive power during childhood.[8, 9] In contrast, AL increases during childhood and in the teenage years, leading to myopia if this growth in AL exceeds the eye's focal point.[10] High myopia, which is defined as spherical equivalent (SE) of -6D or worse, generally corresponds to AL ≥ 26 mm, which drastically increases the risk of severe complications later in life, including myopic maculopathy, retinal detachment, and glaucoma.[11-13] High myopia in adulthood usually has a myopia onset before the age of 10, which progresses during teenage years and early twenties[14-17]; therefore, the ability to identify young at-risk children would provide clinicians the opportunity to apply preventative measures in order to minimise further increases in AL.[18] These measures can include changes in lifestyle (e.g., increasing outdoor exposure[19]), pharmacological agents such as atropine[20, 21], and optical applications such as multifocal contact lenses.[22]

Normative values as a function of age are available for a variety of measurements such as height, weight, and birth weight, and these values are generally visualised using percentile curves. These curves are a powerful tool used by clinicians for sensitively detecting aberrant growth at an early age. Percentile curves for most body measurements, such as height and weight for gestational age, and height in childhood, have been generated using cross-sectional data from extremely large cohorts[23, 24]; however, no such normative data currently exist for ocular biometry components or refractive error.

The aim of this study was to generate a growth chart for AL based on large epidemiological cohorts of European children and adults. We assessed the risk of developing myopia and/or high myopia per percentile, and we examined how growth curves from Western Europe relate axial length measurements in other geographic regions.

METHODS

Study population

The study included three population-based studies: the Generation R study, the Avon Longitudinal Study of Parents and Children (ALSPAC), and the Rotterdam Study III (RS-III).

The Generation R study

The Generation R study is a population-based prospective cohort study of pregnant women and their subsequent children, conducted in Rotterdam, the Netherlands. The complete methodology for this study has been described elsewhere.[25, 26] In brief, a total of 9,778 pregnant women were included in the study, and their children were born from April 2002 through January 2006. At 6 and 9 years of age, the children were invited for an examination by trained nurses at a research centre. From the initial cohort, 6,690 (68.4%) children participated in the physical examination at 6 years of age, and 5,862 (60.0%) participated at 9 years of age. Follow-up data regarding AL were available for 4,787 children at both ages.

The Avon Longitudinal Study of Parents and Children

ALSPAC is a prospective population-based birth cohort study based in the former Avon health authority area in Southwest England. This study was designed to investigate the determinants for development, health, and disease in childhood and adulthood. Subject recruitment for this study has been described previously.[27] In brief, pregnant women with an expected date of delivery from 1 April, 1991 through 31 December, 1992 were eligible to participate, and 14,541 eligible women were recruited. These pregnancies resulted in 14,062 live births, and 13,988 of the infants were still alive at 1 year of age. Eye examinations were performed in these children from 7 years of age onwards, and ocular biometry measurements were included at age 15.

The Rotterdam Study III

RS-III is a prospective, population-based cohort study of subjects ≥ 45 years of age living in Ommoord, a suburb of Rotterdam, the Netherlands. In this study, researchers examined cardiovascular, endocrine, neurological, respiratory, and ophthalmic outcomes. Baseline examinations – including best-corrected visual acuity and refractive error measurements – were performed from 2006 through 2008. AL was measured in a random subset of the RS-III cohort at baseline and in a different random subset during follow-up examinations in 2011-2012.[28]

Ethical approval

Written informed consent was obtained from all participants or parents in all three cohorts.

The study protocols for the Generation R study and RS-III were approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam, the Netherlands. Ethics approval for the ALSPAC study was obtained from the Law and Ethics Committee and the respective local research ethics committees (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary). All research was conducted in accordance with the Declaration of Helsinki.

Data collection

In the Generation R and ALSPAC studies, ocular biometry was measured using a Zeiss IOL Master 500 (Carl Zeiss, Jena, Germany or Welwyn Garden City, UK). In RS-III, AL was measured using an A-scan ultrasound device (Pacscan 300AP, Sonomed Escalon, MEyeTech GmbH, Hardegsen Germany) or LenStar device (Laméris Ootech, Haag-Streit, UK). Corneal curvature was measured using a Topcon RM - A2000 auto-refractor (Topcon Optical Company, Tokyo, Japan). For measuring AL, five measurements were obtained per eye and were then averaged to obtain a mean AL value. For the corneal radius three measurements of K1 and K2 were obtained per eye and averaged to obtain a mean corneal radius of curvature (CR). AL/CR ratio was calculated by dividing AL (in mm) by CR (in mm).

To calculate axial elongation and the change in corneal radius in mm/year, and the change in AL/CR ratio in mm/year, the measurement at 6 years of age was subtracted from the measurement at 9 years of age, and divided by the number of years between the two measurements. Refractive error was available in Generation R at 9 years and in the Rotterdam Study III. In the Generation R cohort, automated cycloplegic refraction was measured in a random subsample at 9 years of age using a Retinomax-3 device (Bon, Lübeck, Germany). At least thirty minutes prior to measuring refractive error, 2 drops (3 with dark irises) of cyclopentolate (1%) were administered, and a pupil diameter ≥ 6 mm was required before SE was determined. SE was calculated as the average sphere + 1/2 cylinder for both eyes. In the RS-III cohort, refraction was measured objectively using a Topcon RM-A2000 (Topcon Optical company, Tokyo, Japan), and then subjectively adjusted with +0.25D or -0.25D steps, spherically as well as cylindrically to achieve the best possible visual acuity. Myopia was defined as SE of ≤ -0.5D, emmetropia was defined as SE between -0.5D and +2.0D, and hyperopia was defined SE ≥ +2.0D. At the age of 6 years in Generation R, cycloplegic refractive error was only obtained when visual acuity was worse than 0.2 LogMAR, detecting myopia ≤ -0.5 but not hyperopia; we therefore did not use refractive error data at age 6 for analyses. In contrast, cycloplegic refractive error was collected in all 9-year-olds, and non-cycloplegic refraction was collected in all adults.

Statistical methods

Average values of AL, CR, and AL/CR were calculated. Differences between genders were analysed using the Students test or the chi-square test. The association between biometry variables and SE were determined using linear regression models. For the growth curves of AL and AL/CR, we used the 2nd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 98th percentile values for the children in the Generation R and ALSPAC studies, with the measurements in the RS-III cohort as the final refractive state in adults. AL was plotted against age, and an interpolation line was created between the matching percentiles of each age. Individual percentiles for AL at 6 and 9 years of age were calculated relative to the entire cohort, and the absolute difference between 6 and 9 years was calculated. To test for concordance of our results with other studies conducted in other geographic regions, we extracted data from 15 other population-based and school-based studies that were conducted in North America[10], Europe[29-31], Asia[9, 32-36], and Australia and Vanuatu[37-39] for which gender-stratified data were available. The association between SE and either AL or AL/CR ratio was determined using linear regression models and ordinary least squares linear regression models, with restricted cubic splines with three knots (the 10th, 50th, and 90th percentiles) in the 9-year-old children in the Generation R cohort. All models were adjusted for both age and gender. Ordinary least squares linear regression models were generated using the program R; all other statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY).

RESULTS

Ocular biometry and refractive error

Analyses were performed at the cohort level. In the Generation R cohort, complete ocular biometry data were available for 6084 and 5295 children at 6 and 9 years of age, respectively. In the ALSPAC cohort, complete ocular biometry data were available for 2495 children 15 years of age. In the RS-III cohort, data were available for 2957 adults with a mean age of approximately 57 years. The general demographic characteristics of all participants in all four age categories are shown in Table 1. In the children 6 and 9 years of age, mean (SD) AL was 22.36 (0.75) and 23.10 (0.84) mm, respectively. AL was 23.41 (0.86) mm in the 15-year-olds and 23.67 (1.26) mm in the adults. Among all four cohorts, the minimum and maximum AL values were 17.54 and 30.12 mm, respectively. Mean (SD) CR was 7.77 (0.26) and 7.78 (0.26) mm in the 6-year-old and 9-year-old children, respectively, 7.82 (0.27) mm in the 15-year-olds, and 7.74 (0.26) mm in the adults, and among all four cohorts, the minimum and maximum CR values were 6.91 and 9.61 mm, respectively. The mean (SD) AL/CR ratio was 2.88 (0.08) in the 6-year-olds and 3.05 (0.15) in the adults; among all four cohorts, the minimum and maximum AL/CR values were 2.38 and 4.07, respectively. On average, the females in each age group had significantly shorter AL, steeper CR, and lower AL/CR ratios compared to the males in their respective age groups ($p < 0.001$). The gender-stratified mean and SD values for general and ocular characteristics are shown in Table 1. Height had the strongest correlation with AL in the 6-year-old group ($\beta = 0.028$; $p < 0.001$), and this correlation decreased slightly – but remained significant – in the 9-year-old group ($\beta = 0.024$; $p < 0.001$). No significant difference in height was found between the refractive error groups in boys (ANOVA $p = 0.40$) as well as girls (ANOVA $p = 0.24$).

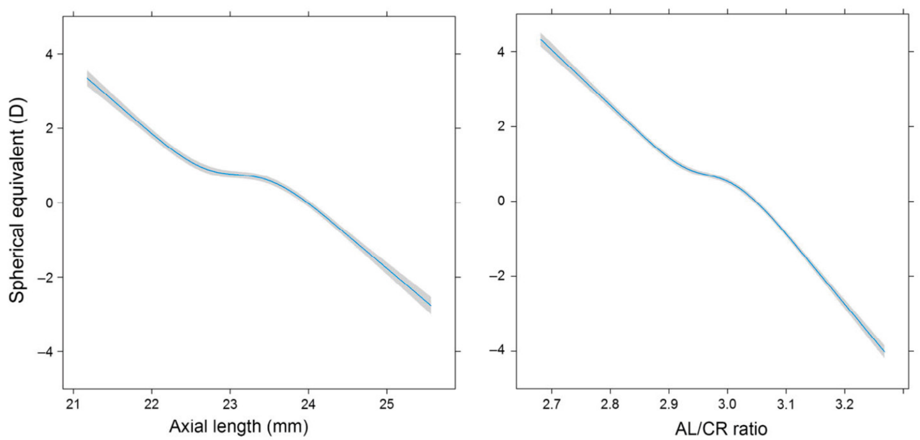

Figure 1: Association between spherical equivalent (in dioptres) and axial length (AL) (in mm; left) and AL/corneal radius of curvature ratio (right) at 9 years of age. The mean and 95% CI were adjusted for age, gender and height.

Table 1. General and ocular characteristics of the four study cohorts.

	All	Male	Female	*P*-value[2]
Generation R at 6 years of age (N = 6084)				
Age in years	6.17 (0.52)	6.18 (0.55)	6.16 (0.50)	0.03
Gender, N (%)	6084 (100)	3033 (49.9)	3051 (50.1)	NA
European ethnicity, N (%)	3983 (65.5)	1965 (64.8)	2018 (66.1)	0.27
Height in cm	119 (6)	120 (6)	119 (6)	<0.001
European ethnicity, N (%)	4089 (67.2)	2023 (66.7)	2066 (67.7)	0.41
Axial length in mm	22.36 (0.75)	22.63 (0.73)	22.09 (0.7)	<0.001
Corneal radius in mm	7.77 (0.26)	7.84 (0.26)	7.70 (0.24)	<0.001
AL/CR ratio	2.88 (0.08)	2.89 (0.08)	2.87 (0.08)	<0.001
Generation R at 9 years of age (N = 5296)				
Age in years	9.79 (0.33)	9.80 (0.36)	9.77 (0.31)	0.02
Gender, N (%)	5296 (100)	2617 (49.4)	2679 (50.6)	NA
European ethnicity, N (%)	3770 (71.2)	1842 (70.4)	1928 (72.0)	0.21
Height in cm	142 (6)	142 (6)	141 (7)	0.05
Axial length in mm	23.10 (0.84)	23.36 (0.82)	22.84(0.78)	<0.001
Corneal radius in mm	7.78 (0.26)	7.85 (0.26)	7.72 (0.24)	<0.001
AL/CR ratio	2.97 (0.09)	2.98 (0.10)	2.96 (0.09)	<0.001
SE in dioptres[1]	0.74 (1.30)	0.73 (1.28)	0.75 (1.31)	0.66
ALSPAC cohort (N = 2495)				
Age in years	15.47 (0.32)	15.45 (0.29)	15.49 (0.34)	0.001
Gender, N (%)	2495 (100)	1167 (46.7)	1328 (53.3)	NA
European ethnicity, N (%)	2447 (98.1)	1145 (98.1)	1302 (98.0)	0.79
Height in cm	169 (8)	175 (7)	165 (6)	<0.001
Axial length in mm	23.41 (0.86)	23.68 (0.88)	23.18 (0.84)	<0.001
Corneal radius in mm	7.82 (0.27)	7.88 (0.27)	7.77 (0.25)	<0.001
AL/CR ratio	2.99 (0.1)	3.01 (0.1)	2.98 (0.10)	<0.001
	All	**Males**	**Females**	***P*-value[2]**
RS-III cohort (N = 2957)				
Age in years	56.8 (6.4)	56.8 (6.3)	56.8 (6.3)	0.83
Gender, N (%)	2957 (100)	1290 (43.6)	1667 (56.4)	NA
European ethnicity, N (%)	2745 (92.8)	1215 (94.2)	1530 (91.8)	0.01
Height in cm	170.5 (10)	178 (6)	164 (7)	<0.001
Axial length in mm	23.67 (1.26)	23.99 (1.26)	23.42 (1.20)	<0.001
Corneal radius in mm	7.74 (0.26)	7.81 (0.25)	7.69 (0.25)	<0.001
AL/CR ratio	3.05 (0.15)	3.07 (0.16)	3.04 (0.15)	<0.001
SE in dioptres	-0.31 (2.5)	-0.39 (2.5)	-0.26 (2.5)	0.16

Notes: Except where indicated otherwise, all data are presented as the mean (SD). AL, axial length; CR, corneal radius of curvature; SE, spherical equivalent.
[1]N = 2408 (1204 males and 1204 females).
[2]*P*-values were calculated using the Student's *t*-test or the chi-square test.

Table 2. Ocular biometry and correlation with spherical equivalent (SE) in children and adults.

	Children at 9 years of age (N = 2408)		Adults ≥ 45 years of age (N = 2957)	
	Mean (SD; 90% range)	**β (95% CI) of association with SE**	**Mean (SD, 90% range)**	**β (95% CI) of association with SE**
Axial length (mm)				
All	23.10 (0.81; 21.79 – 24.42)	-1.06 (-1.12 – -1.01)	23.67 (1.26; 21.82 – 25.90)	-1.61 (-1.66 – -1.56)
Hyperopia	22.08 (0.69; 21.20 – 23.28)	-0.82 (-1.02 – -0.62)	22.30 (0.90; 20.70 – 23.72)	-1.04 (-1.16 – -0.91)
Emmetropia	23.08 (0.67; 22.02 – 24.23)	-0.25 (-0.28 – -0.21)	23.30 (0.85; 21.95 – 24.71)	-0.23 (-0.23 – -0.19)
Myopia	23.98 (0.83; 22.75 – 25.37)	-0.98 (-1.15 – -0.82)	24.62 (1.19; 22.86 – 26.58)	-1.24 (-1.34 – -1.16)
P-value	<0.001		<0.001	
Corneal radius of curvature (mm)				
All	7.78 (0.25; 7.38 – 8.22)	0.70 (0.49 – 0.91)	7.74 (0.26; 7.33 – 8.18)	1.10 (0.74 – 1.46)
Hyperopia	7.80 (0.26; 7.38 – 8.26)	1.11 (0.52 – 1.69)	7.79 (0.25; 7.39 – 8.23)	0.13 (-0.47 – 0.74)
Emmetropia	7.79 (0.25; 7.39 – 8.22)	0.19 (0.01 – 0.29)	7.75 (0.26; 7.33 – 8.20)	0.12 (-0.13 – 0.24)
Myopia	7.73 (0.25; 7.38 – 8.26)	0.63 (-0.05 – 1.31)	7.72 (0.26; 7.30 – 8.15)	0.44 (-0.05 – 0.93)
P-value	<0.001		0.008	
AL/CR ratio				
All	2.97 (0.09; 2.84 – 3.13)	-11.56 (-11.89 – -11.23)	3.05 (1.51; 2.83 – 3.32)	-14.43 (-14.73 – -14.13)
Hyperopia	2.83 (0.08; 2.40 – 3.01)	-9.77 (-10.91 – -8.62)	2.86 (0.11; 2.69 – 3.02)	-9.94 (-10.96 – -8.92)
Emmetropia	2.96 (0.06; 2.87 – 3.06)	-4.43 (-4.76 – -4.11)	3.01 (0.08; 2.87 – 3.14)	-3.35 (-3.73 – -2.97)
Myopia	3.10 (0.09; 2.97 – 3.25)	-11.07 (-12.24 – -9.90)	3.19 (0.14; 3.00 – 3.42)	-12.43 (-13.03 – -11.84)
P-value	<0.001		<0.001	
Axial length growth (mm/year)				
All	0.21 (0.08; 0.11 – 0.37)	-10.54 (-11.05 – -10.04)	NA	NA
Hyperopia	0.15 (0.06; 0.06 – 0.26)	-5.01 (-7.31 – -2.71)	NA	NA
Emmetropia	0.19 (0.05; 0.12 – 0.29)	-3.64 (-4.07 – -3.21)	NA	NA
Myopia	0.34 (0.11; 0.17 – 0.53)	-5.86 (-7.30 – -4.44)	NA	NA
P-value	<0.001		NA	
Corneal radius of curvature growth (mm/year)				
All	0.004 (0.01; NA0.010 – 0.015)	1.46 (-3.60 – 6.52)	NA	NA
Hyperopia	0.003 (0.01; -0.010 – 0.015)	4.80 (-7.79 – 17.40)	NA	NA
Emmetropia	0.004 (0.01; -0.009 – 0.015)	-0.42 (-2.69 – 1.85)	NA	NA
Myopia	0.003 (0.01.; -0.013 – 0.015)	-3.34 (-21.07 – 14.39)	NA	NA
P-value	0.37		NA	
AL/CR change (units/year)				
All	0.025 (0.011; 0.012 – 0.046)	-72.73 (-76.55 – -68.92)	NA	NA

Notes: Except where indicated otherwise, all data are presented as the mean (SD). AL, axial length; CR, NA, not applicable (no follow-up data were available); SE, spherical equivalent. Sample size in the refractive error categories at 9-year-old: hyperopia, N = 203; emmetropia, N = 1926; myopia, N = 279. Sample size in the refractive error categories in the adults: hyperopia, N = 352; emmetropia, N = 1512; myopia N = 1093. In the regression models, SE was used as the dependent variable, and the ocular biometry measurements were used as the independent variable. The models were adjusted for age, gender, ethnicity, and height. P-values reflect the differences in ocular biometry measurements between the refractive groups and were calculated using an ANOVA.

Refractive error had a relatively narrow distribution in both the 9-year-olds and the adults (Supplemental Figure S1), with mean SE values of +0.74D (SD: 1.30; range: -9.8D to +8.3D) and -0.31D (SD: 2.53; range:-13.8D to +9.1D), respectively. At 9 years of age, there was no significant difference in SE between boys and girls (mean SE was +0.73D and +0.75D, respectively; p = 0.66); we also found no significant difference between the adult males and females (-0.39D vs. -0.26D, respectively; p = 0.16). Among the 9-year-old children, 11.4% (N = 274) and 8.4% (N = 203) had myopia and hyperopia, respectively; among the adults, 37.0% (N = 1093) and 11.9% (N = 352) had myopia and hyperopia, respectively.

Table 2 summarises the differences in ocular biometry and the association between SE and the various refractive error groups in the Generation R and RS-III cohorts. Our analysis revealed that SE was inversely correlated with both AL and the AL/CR ratio in both the Generation R (Figure 1) and RS-III cohorts. Interestingly, the relationship between SE and AL/CR ratio was non-linear (quadratic term p <0.001). The correlation between SE and both AL and AL/CR ratio was weakest in the emmetropic participants and strongest in the myopic participants (Table 2).

In addition, SE was significantly correlated with CR. On average, the myopic children had a steeper CR (7.73 mm) compared to both the emmetropic (7.79 mm; p = < 0.001) and hyperopic (7.80 mm; p = < 0.001) children. Similar results were obtained in the adult cohort (Table 2).

Longitudinal changes in AL were also measured in the Generation R cohort between the 6-year-old and 9-year-old children. On average, AL increased by 0.21 mm/year (SD: 0.08 mm/year), and the AL/CR ratio increased by 0.025 units/year (SD: 0.011 units/year). The myopic children had more rapid eye growth rate (0.34 mm/year) than both the emmetropic (0.19 mm/year; p < 0.001) and hyperopic (0.15 mm/year; p < 0.001) children. At 9 years of age, the increases in AL and AL/CR ratio were significantly associated with a shift in refractive error towards increased myopia; this result was present in all refractive error categories. We found no significant change in CR from 6 to 9 years of age (Table 2).

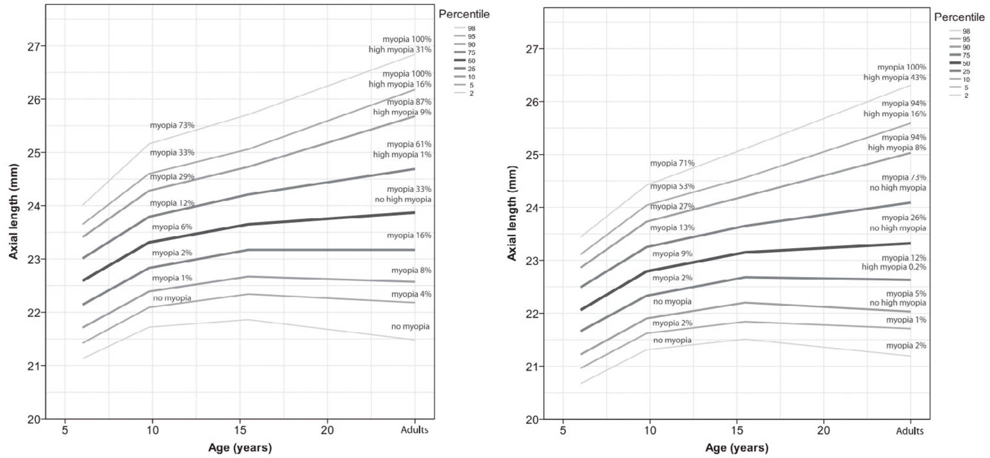

Figure 2: Growth chart depicting axial length (in mm) versus age for European study subjects, males (left) and females (right), with the risk of myopia in adulthood. The myopia percentage represents the proportion of myopia in halfway above and below the percentage line.

AL growth curves

Figure 2 shows the growth chart for AL versus age in percentiles. From 6 to 9 years of age, all of the percentiles examined increased in AL; however, none of the percentiles below the median increased further after the age of 15. In particular, the lowest percentiles of AL increased relatively little after the age of 6, and the 5th percentile values changed by less than 1 mm with age. The AL of all of the median and above-median percentiles increased until adulthood. The median percentile in the male participants increased by 1.28 mm (22.59 mm vs. 23.87 mm at 6 years of age and adulthood, respectively; Figure 2 and (Supplementary Table S1a), and the 95th percentile increased by 2.5 mm (23.65 mm vs. 26.18 mm at 6 years of age and adulthood, respectively). Similar results were observed for AL in the female participants (Figure 2 and Supplementary Table S1b) and for the AL/CR ratio in both genders (Supplementary Figure S2). The above-median percentiles of AL were associated with a > 50% risk of developing myopia in adulthood age; moreover, the highest 10th percentile was associated with a 97% risk of myopia and a 23% risk of high myopia. CR was relatively consistent across all age groups (Supplementary Figure S3).

The median absolute difference in AL was 5.6 percentiles (IQR: 2.4–11.2), indicating that a given child's percentile at age 6 is a reliable predictor of that child's percentile at age 9. Moreover, we found a significant correlation in percentile position between 6 and 9 years of age (Spearman correlation coefficient: 0.92; p <0.001). Higher change in percentile position was highly correlated to myopia prevalence (figure 4).

Of the 354 children who had an increase in percentile score of ≥ 10, 45.8% (N = 162) were myopic at 9 years of age; in contrast, only 4.8% (85/1781) of the children who had an increase in percentile score < 10 were myopic at 9 years of age.

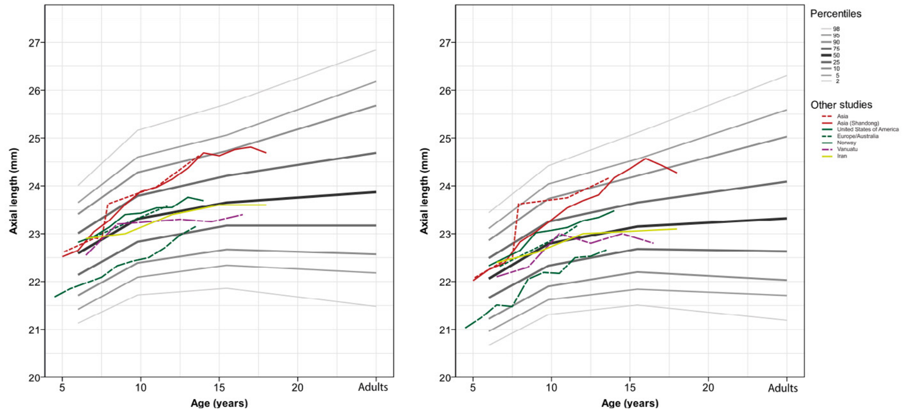

Figure 4: Axial length is plotted against age for male (left) and female (right) children from various geographic locations. For comparison, the data from the present study are copied from Fig. 2 and are shown here in grey. Gender-stratified data were collected from Australia, Europe, the United States, Iran, Vanuatu and Norway. The European and Australian children were clustered as being predominantly of European descent. Solid lines are single studies, dashed line multiple studies from the same geographic regions and irregular dashed lines single studies published before 1990.

Support for our growth curves based on previous publications

Finally, we used gender-stratified AL measurements obtained from published population-based and school-based studies in order to confirm our growth curves. As shown in Figure 3, the median AL growth rates in studies of European children were similar to our own median values. The mean AL value in Asian populations was larger after 7 years of age. In addition, the mean AL values in the children measured in both Vanuatu study and in an older study of Norwegian children were smaller than our median value.[29, 37]

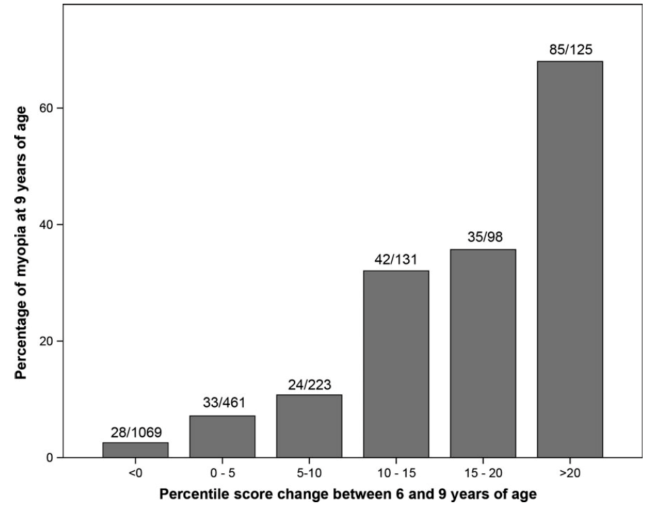

Figure 3: The change in percentile score of axial length between 6 and 9 years of age (x-axis) and the percentage of myopia at 9 years of age (y-axis).

DISCUSSION

The aim of this study was to provide normative growth values for ocular biometry and the associated risk of developing myopia in European children. Our analysis revealed that median AL increased with age until 15 years of age, after which AL continued to increase into adulthood in the top 50th percentile. CR was relatively similar across age groups, with only a slightly smaller corneal radius in the adult cohort. At 9 years of age, the children in the European cohorts were generally emmetropic, with an average SE of +0.74 D, and 11.4% of these children were already myopic. The correlation between SE and AL/CR ratio and was not linear as a whole; rather, it was weaker around the emmetropic values. This was likely due to compensation by other optical features such as the crystalline lens and anterior chamber depth.[40]

Our study has several strengths. First, we included more than 12,000 measurements of ocular biometry in European children and adults in four discrete age categories. Second, the studies from which we collected our data used auto refraction to measure refractive error. Third, the age ranges of the children were extremely narrow, allowing for highly robust analysis. Finally, the data were stratified by gender.

Despite these strengths, several possible weaknesses warrant discussion. First, the ALSPAC study involving 15-year-old children was conducted in the UK, whereas the Generation R and RS-III studies were conducted in the Netherlands; therefore, geographic and/or other factors may have affected our analysis. Second, we lacked a study population of young adults, and actual measurements of refractive error for ages

20-25 years would have corrected for small alternations of axial length changes from early to late adulthood, whereas most of the axial elongation will occur between 15-25 years of age.[41] Third, the birth years differed among the three cohorts, and younger cohorts may have a higher risk of myopia in adulthood compared to older cohorts.[6, 7] Such a cohort effect may have led to an underestimation of the upward trend of the growth curve at age 15 and older. Fourth, differences inthe instruments used (e.g., IOL Master vs. keratometry/A-scan ultra sonography) for the various cohorts may have generated a systematic error in biometry measurements. Although AL measurements do not differ between instruments, CR values can differ by up to 0.03 mm between Topcon Keratometry and IOL Master.[42-47] Lastly, the published studies predominantly reported mean AL values, rather than median AL values. However, this likely had only had a slight effect on the trajectories, as the difference mean and median AL values was relatively low (0.03 – 0.12 mm) in all of our study cohorts.

Our findings are similar to other cohort data in several respects. First, we observed a gender difference in AL, CR, and AL/CR ratio, which is consistent with previous observations.[30, 34, 38, 48] In addition, we found that AL increased more rapidly in the myopic children than in the children with hyperopia, a finding consistent with the NICER (Northern Ireland Childhood Errors of Refraction) study.[49] We also compared the AL growth rates in our study with data obtained from other geographic regions and found several interesting ethnic and cohort effects. For example, children in East Asia generally have higher AL after the age of 6 years compared to both European and Iranian children, reflecting higher risk for developing myopia.[30, 31, 33, 38] Compared to the 6-year-old children in our Dutch study, 3-year-old Asian children have shorter AL and lower AL/CR ratios, but similar CR values.[50] At 5 years of age, children in Singapore had similar AL values as the 6-year-old children in our study[32]; however, at 8 years of age, the children in Singapore had longer AL values and higher AL/CR ratios than our 9-year-old children. In contrast, compared with our results, Northern European children in a study conducted in 1971 had lower AL values at all ages[29], which can be caused by a lower myopia prevalence as well as a lower body height, or a combination of these.

The prevalence of myopia among European children has only been examined in relatively few studies.[2, 3, 51] The multi-ethnic CHASE (Child Heart and Health Study in England) study in the UK reported a prevalence of 11.9% (≤ -0.50D) at approximately 11 years of age[30], and the NICER study in Northern Ireland reported a prevalence of 17.7% (≤ -0.50D) at approximately 13 years of age.[52] The multi-ethnic CLEERE (Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error) study conducted in the US found a prevalence of 11.6% (≤ -0.75D in both meridians) in 10-year-olds[10], and the Australian Sydney Myopia Study found a prevalence of 11.9% (≤ -0.50D) in 13-year-olds.[39] These values are similar to the prevalence of 11.4% that we found in our Dutch cohort of 9-year-olds. We and others have found that height is associated with axial length, and this needs to be taken into account when interpreting the growth curves.

Interestingly, our analysis revealed a large difference in eye growth between children at risk for developing myopia and children with low risk; specifically, the rate of eye growth was twice as high in the children who developed myopia compared to the children who remained hyperopic. Follow-up studies are needed to determine whether children born after 2010 have a steeper growth curve than suggested by our growth chart. In addition, the growth curves can be improved further by focussing on children who differ in ages from those in our study, thereby providing complementary data.

CONCLUSIONS

Our normative data regarding AL may serve as a key instrument for monitoring eye growth in children with progressive myopia in European and other populations. Paediatric ophthalmologists, optometrists, and orthoptists can use these charts to determine whether a child's axial length is above average for his/her age, and this information can be used to estimate the risk of developing high myopia. In addition, children with a rate of AL growth higher than expected based on their percentile line can be identified relatively early, allowing these children to benefit from the increasing number of therapeutic options for preventing myopia.

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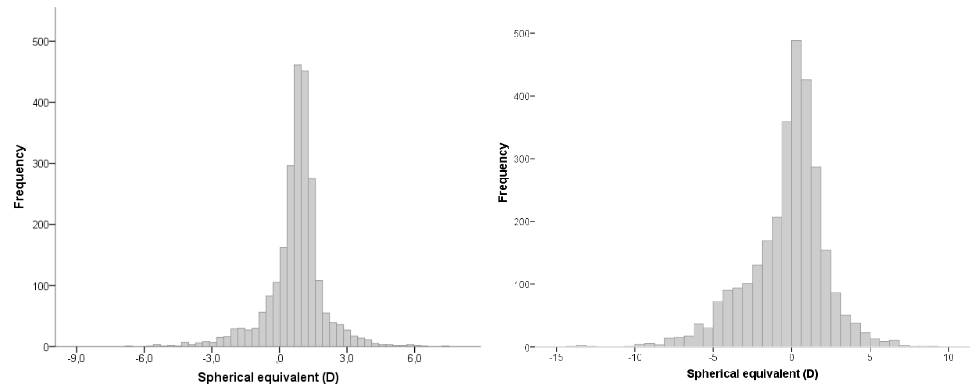
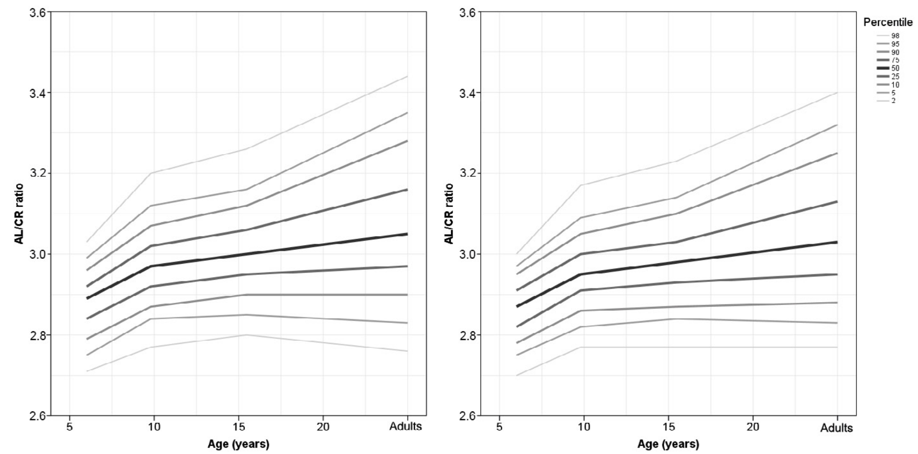
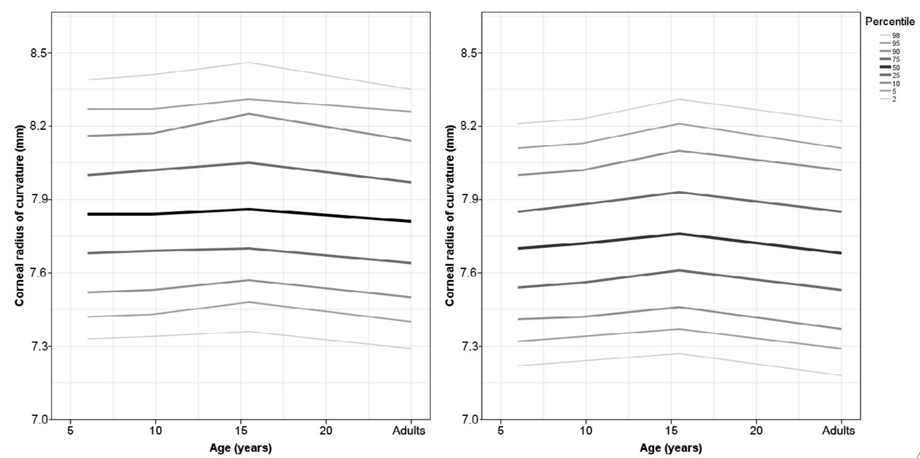
Supplementaries



Supplementary Figure S1. *Distribution of refractive error at age 9 years (left) and in adults (right)*



Supplementary Figure S2. *AL/CR as a function of age in boys (left) and girls (right)*



Supplementary Figure S3. *CR as a function of age boys (left) and girls (right)*

Supplementary Table S1a Percentiles of axial length, corneal radius and AL/CR ratio in 6 and 9 year old European boys

Percentile	AL	CR	AL/CR ratio
6 years visit (N = 1965)			
2	21.13	7.33	2.71
5	21.42	7.42	2.75
10	21.71	7.52	2.79
25	22.14	7.68	2.84
50	22.59	7.84	2.89
75	23.01	8.00	2.92
90	23.41	8.16	2.96
95	23.65	8.27	2.99
98	24.01	8.39	3.03
9 years visit (N = 1842)			
2	21.72	7.34	2.77
5	22.09	7.43	2.84
10	22.39	7.53	2.87
25	22.83	7.69	2.92
50	23.31	7.84	2.97
75	23.79	8.02	3.02
90	24.28	8.17	3.07
95	24.60	8.27	3.12
98	25.16	8.41	3.20
15 years (ALSPAC; N = 1145)			
2	21.86	7.36	2.80
5	22.34	7.48	2.85
10	22.67	7.57	2.90
25	23.17	7.70	2.95
50	23.65	7.86	3.00
75	24.21	8.05	3.06
90	24.73	8.25	3.12
95	25.06	8.31	3.16
98	25.71	8.46	3.26
45+ years visit (RS III; N = 1215)			
2	21.48	7.29	2.76
5	22.18	7.40	2.83
10	22.57	7.50	2.90
25	23.17	7.64	2.97
50	23.87	7.81	3.05
75	24.69	7.97	3.16
90	25.68	8.14	3.28
95	26.18	8.26	3.35
98	26.84	8.35	3.44

Supplementary Table S1b. Percentiles of axial length, corneal radius and AL/CR ratio in 6 and 9 year old European girls

Percentile	AL	CR	AL/CR ratio
6 years visit (N = 2018)			
2	20.67	7.22	2.70
5	20.96	7.32	2.75
10	21.22	7.41	2.78
25	21.66	7.54	2.82
50	22.06	7.70	2.87
75	22.49	7.85	2.91
90	22.86	8.00	2.95
95	23.11	8.11	2.97
98	23.44	8.21	3.00
9 years visit (N = 1928)			
2	21.31	7.24	2.77
5	21.62	7.34	2.82
10	21.90	7.42	2.86
25	22.33	7.56	2.91
50	22.79	7.72	2.95
75	23.25	7.88	3.00
90	23.73	8.02	3.05
95	24.04	8.13	3.09
98	24.42	8.23	3.17
15 years visit (ALSPAC; N = 1302)			
2	21.51	7.27	2.77
5	21.84	7.37	2.84
10	22.20	7.46	2.87
25	22.68	7.61	2.93
50	23.15	7.76	2.98
75	23.65	7.93	3.03
90	24.21	8.10	3.10
95	24.56	8.21	3.14
98	25.11	8.31	3.23
RS III 45+ years visit (N = 1530)			
2	21.19	7.18	2.77
5	21.71	7.29	2.83
10	22.03	7.37	2.88
25	22.63	7.53	2.95
50	23.32	7.68	3.03
75	24.09	7.85	3.13
90	25.03	8.02	3.25
95	25.59	8.11	3.32
98	26.31	8.22	3.40

3.2

Myopia progression from wearing first glasses to adult age: the DREAM study

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Myopia progression from wearing first glasses to adult age: the DREAM study

ABSTRACT

Purpose: Data on myopia progression during its entire course are scarce. The aim of this study is to investigate myopia progression in Europeans as a function of age and degree of myopia from first prescription to final refractive error.

Methods: The Drentse Refractive Error and Myopia Study assessed data from a branch of opticians in the Netherlands from 1985 onwards in a retrospective study. First pair of glasses prescribed was defined as a spherical equivalent of refraction (SER) ≤ -0.5D to ≥ -3.0D. Subjects with prescriptions at an interval of at least one year were included in the analysis.

Results: A total of 2555 persons (57.3% female) met the inclusion criteria. Those with first prescription before the age of 10 years showed the strongest progression (-0.50D; IQR: -0.75 to -0.19) and a significantly ($p < 0.001$) more negative median final SER (-4.48D; IQR: -3.42 to -5.37). All children who developed SER ≤ -3D at 10 years were highly myopic (SER ≤ -6D) as adults, children who had SER between -1.5D and -3D at 10 years had 46.0% risk of high myopia, and children with SER between -0.5D and -1.5D had 32.6% risk of high myopia. Myopia progression diminished with age; all refractive categories stabilized after age 15 years except for SER ≤ -5D who progressed up to -0.25D annually until age 21 years.

Conclusion: Our trajectories of the natural course of myopia progression may serve as a guide for myopia management in European children. SER at 10 years is an important prognostic indicator and will help determine treatment intensity.

INTRODUCTION

The current worldwide increase in myopia prevalence is leading to a growing public health burden, as the more high levels of myopia (≤ -6D) can lead to blinding complications such as myopic macular degeneration, retinal detachment, glaucoma and choroidal neovascularisation.[1-3] Risk factors for high myopia at adult age are a young age of onset and a fast progression rate during childhood.[4-6]

Myopia onset occurs typically during childhood, teenage years or adolescence.[4, 7] The average age of myopia onset varies among gender, ethnicities, and presence of parental myopia.[8] Other established risk factors for myopia are more intense education, less time outdoors, and increased near work that appear to coincide with an earlier onset.[9-12] The strongest progression of eye growth is observed in early childhood, while stabilisation may not occur untillate adolescence.[13, 14] Around 90% of all myopic individuals appear to be stable at the age of 21 years, and nearly all by the age of 24 years.[8]

Most existing data on myopia progression have been provided by controlled myopia intervention studies,which have a short follow-up period, limited numbers or are based on imputed data.[8, 15, 16] Longitudinal studies in Europeans with 10 year follow up are available, but time interval between the onset of myopia and final refractive error might be longer. This limits robust insights into the association between age of onset and final refractive error.[17] The aim of this study is to describe myopia growth trajectories and the association between the first myopic prescription and final refractive error in a cohort of European children.

METHODS

Study Population

The Drentse Refractive Error And Myopia (DREAM) Study population comprised of subjects who bought their glasses from 1 of the 14 Dispensing opticians from a chain of stores belonging to 1 family. The stores were located in the north of the Netherlands including the provinces of Overijssel, Friesland, Groningen, and Drenthe. The area has 1.7 million inhabitants and is classified as a non-urban area with 37% of the people living in an urban environment.[18] Ethnicity was an unknown variable in this study, however according to the open source Statistics Netherlands' database, persons in the region with a non-western background was approximately 3% in 1980 to 5% in 2015.[18] Records of eyeglass orders were stored digitally since 1985, and all data gathered since that time up to 2015 entered the current analysis. Eligibility criteria were at least two orders of myopic eye glasses with an interval of 1 year or more until the age of 25 years. Final degree of myopia was obtained from a visit between 22 and 25 years of age. Subjects were born between 1962 and 1997; follow up time ranged from 1 year to 22 years with a mean of 5.82 years (SD 4.1). Data were completely anonymised by the dispensing opticians and in full compliance with the European General Data Protection Regulation. The study was conducted in accordance with the Declaration of Helsinki. Approval for retrospective studies was obtained from the Medical Ethics Committee of the Erasmus MC, who declared that the study does not apply to the Medical Research Involving Human Subjects Act.

Refractive error and myopia

Assessment of refractive error was done by multiple eye care providers however compatible with Dutch health guidelines, refractive error was determined by an orthoptist or an ophthalmologist under cycloplegia up to 12 years of age, and was performed by a qualified optician at older ages. Spherical equivalent of refraction (SER) was calculated as an average sphere + ½ cylinder for both eyes. Myopia was defined as SER of-0.50 D or worse of the prescribed glasses and high myopia was defined as ≤ -6.00D. Contact lens data were used if subjects moved from glasses to contact lenses. The back vertex formula in reversed order was used to calculate the contact lens prescription into those of glasses Fg = Fc / (1 + xFc) in which Fg is the glasses prescription in dioptres, Fc contact lenses prescription and x the vertex distance in meters (0.0125).

Statistical analysis

First purchases of myopic eye glasses with refractive error up to -3D were eligible for the primary analysis; first purchases with more severe myopia were only eligible for myopia progression analyses. Data were presented as medians and IQRs, the percentiles or numbers and percentages. SER and progression rates showed a non-normal distribution, and a nonparametric test was used. Differences in progression between spherical equivalent groups (-1D to -2D; -2 to -3D;-3D to -4D; -4 to -5D; -5D to -6D; -6 to -7D) at baseline were compared using Kruskal Wallis test; differences between female and male progression using Mann-Whitney U test. The association of SER progression at different age intervals in the same children was determined using Spearman's correlation. The mean myopic SER and the percentiles were calculated per age group (< 10 years n = 253; 10-12 y/a n = 562; 13-15 y/a n = 729; 16-18 y/a n = 882; 19-21 y/a n = 1270). The progression in SER from one age group to the subsequent age group was calculated, as were annual progression rates by the ratio between SER progression and time between visits. For the distribution of myopia progression per age category we calculated the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentile values of myopic SER as annual progression. The cumulative risk of incident high myopia (ie, an SER of -6.0D or more) was estimated by Kaplan-Meier product limit analysis stratified for first myopic prescription and SER categories. P-values below 0.05 were considered statistically significant for all statistical tests. All statistical tests were performed by using IBM SPSS Statistics for Windows, V.25.0.

RESULTS

A total of 2555 (57.3% female) subjects were eligible for the progression analyses; 946 (37.0%, 59.2% female) had a first myopic prescription (SER between -0.5 and -3D) and refraction at adult age (22+ years) (supplementary table 1). Median refractive error at adult age for the complete cohort was -2.50D (IQR:-4.01 to -1.5), the proportion of high myopia was 8.9% (n = 113).

Figure 1 shows the progression of SER per age of onset category (n = 946). Earlier first myopic prescription was significantly associated with a higher degree of myopia (p < 0.001) at adult age. The median annual progression of SER decreased with age; this was -0.50D (IQR: -0.75 to -0.19) in ages up to 10 years; -0.38D (IQR: -0.63 to -0.19) at ages 10-12 years; -0.19D (IQR: -0.34 to -0.06) ages 13-15 years; -0.09D (IQR: -0.21 to 0) at ages 16-18 years; and -0.08D (IQR: -0.21 to 0) at ages 19-21 years.

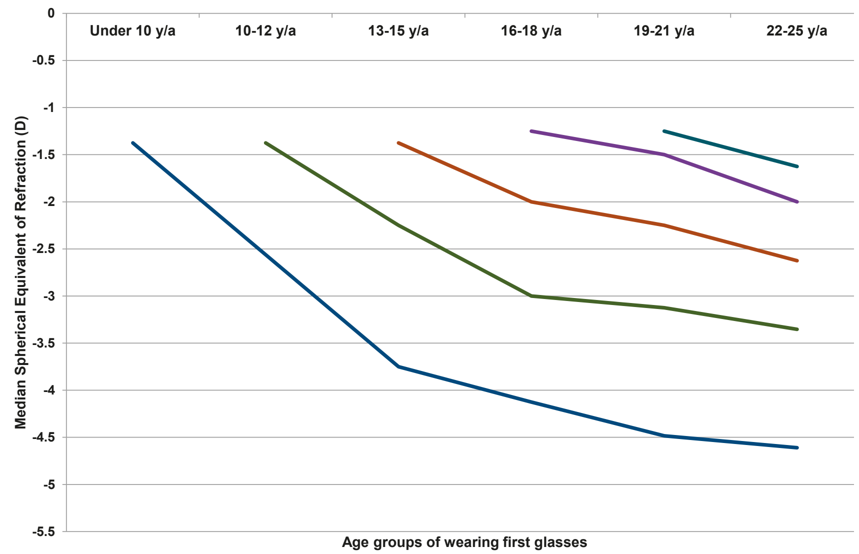

Figure 1: Median spherical equivalent of refraction in dioptres in children from first prescription of myopia and adult myopia obtained at the age of 22–25.

Female subjects showed a significantly stronger progression in only one age category: 19-21 years -0.09D females vs -0.06D males (p = 0.01; figure 2).

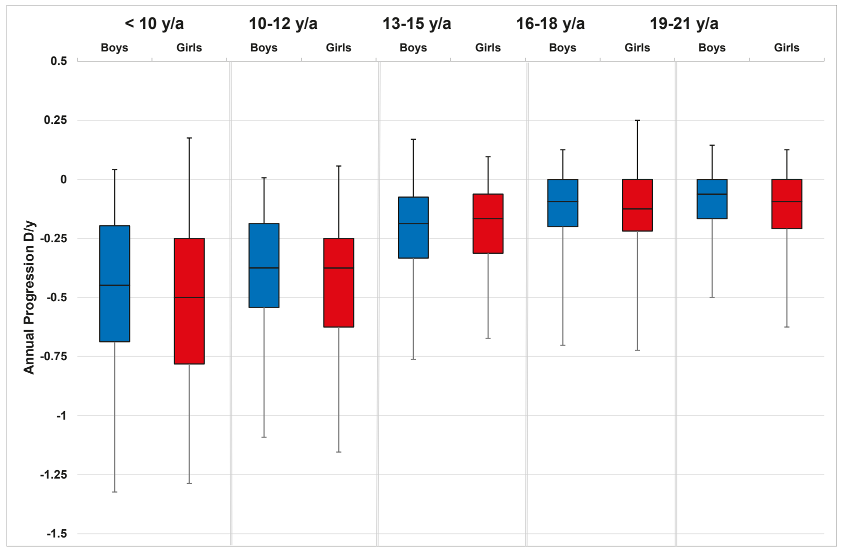

Figure 2: Boxplots of median annual progression of spherical equivalent of refraction in dioptres for boys (blue) and girls (red) per age group. Lower and upper box boundaries 25th and 75th percentiles and lower and upper error lines 2.5th and 97.5th percentiles. Tested with non-parametric Mann-Whitney U test.

Figure 3 shows the annual progression of SER per age category. The annual progression is much greater for those with early onset myopia ≤ 12 years compared with over 12 years. Until 12 years, median progression was more than -0.25D/year; beyond 16 years, only the 90th and 95th percentile progressed more than -0.25D/year.

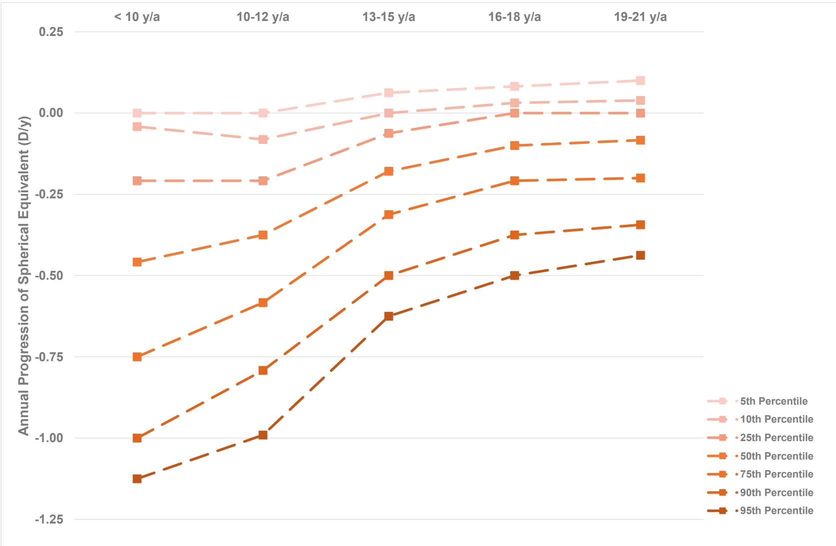

Figure 3: Progression curves in percentiles representing annual progression rate of spherical equivalent in dioptres as a function of age for European myopic subjects. Percentiles were calculated per age group and are connected by dashed lines.

Plots for the median annual progression per age category stratified for adult SER are shown in Figure 4. Subjects with high myopia at adult age had progressed with -0.71D/year (IQR: -0.56 to -0.91) up to age 10 (figure 4F); milder myopes at adult age had progressed at a lower rate in the first decade (figure 4A-E).

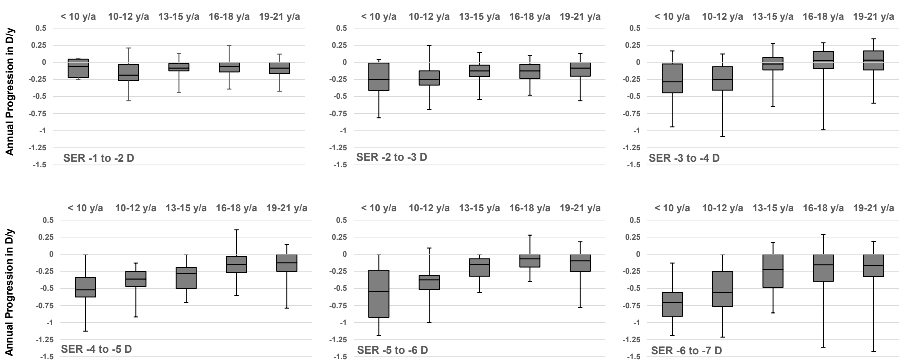

Figure 4: Boxplots of median annual progression in dioptre spherical equivalent per adult degree of myopia category obtained at the age of 22–25. Lower and upper box boundaries 25th and 75th percentiles and lower and upper error lines 2.5th and 97.5th percentiles. SER, spherical equivalent of refraction.

We estimated the risk of high myopia as a function of refractive error in age categories (Figure 5, time to event curve, supplemental table 2). All subjects with SER -3D or worse in childhood up to 10 years developed high myopia. Those with SER -4.5D to -6D at age 10 years developed high myopia at 11.2 y/a (95% CI, 10.0 to 12.5), those with -3D to -4.5D at 10 years did so at 16.0 years (95% CI, 12.9 to 19.0). Remarkably, those with SER -0.5D to -1.5D and -1.5D to -3.0D up to 10 years still had respectively 32.6% and 46.0% risk to develop high myopia by age 25 years; those with SER -0.5D to -1.5D and -1.5D to -3.0D at 10-12 years had only 3.0% and 18.2% risk. Those who had SER -0.5D to -1.5D at later ages had virtually no risk of high myopia. However, those who had moderate myopia, SER -1.5D to -3.0D and -3D to -4.5D, at age 15 years still had 11.8% and 23.2% risk of developing high myopia.

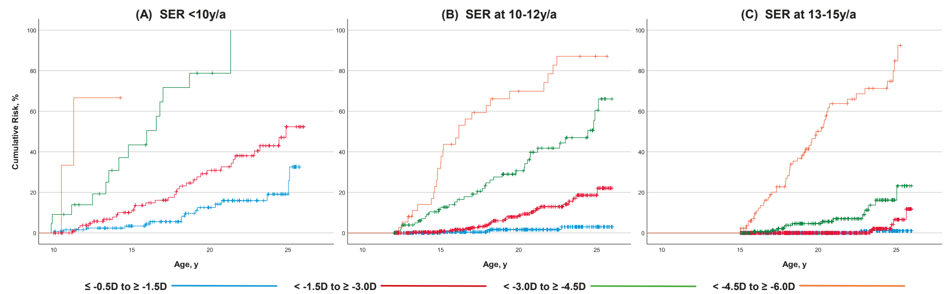

Figure 5 (A–C): Cumulative risk of high myopia (≤ –6D) according to spherical equivalent of refraction in dioptres category by age. (A) For subjects with myopia onset younger than 10 years of age. (B) For subjects with myopia onset 10–12 years of age. (C) For subjects with a myopia onset 13–15 years of age. SER, spherical equivalent of refraction.

Correlation between progression at age < 10 years and at 10-12 years was R = 0.36; between 10-12 years and 13-15 years R = 0.33; between 16-18 years and 19-21 years R = 0.23 (all p ≤ 0.01). Correlation between progression at 13-15 years and 16-18 years was R = 0.13 (p = 0.02).

DISCUSSION

This study describes myopia progression in 2555 European children who received glasses during childhood or teenage years and who were followed until age 25 years. The SER at adult age ranged from -0.5D to -12.75D, with a median of -3.00D. Of those who developed high myopia, 60% had a first pair of glasses before age 10 years. Children who developed -3D or worse in the first decade all developed high myopia. High myopes at adult age had been faster progressors during the entire youth, those with lower refractive errors virtually ceased progression after age 15 years.

Many clinics all over the world are offering myopia control using various strategies. Good myopia management requires insight into the natural course of myopia progression, as the goal is to slow down the rate. Clinical trials have attempted to provide these data by control groups, but the relatively short duration of these studies have hampered long-term predictions. Our study is unique as it studies myopia progression until age 25 years in a very large Dutch cohort. The cohort consisted of individuals who had bought their glasses at a branch of dispensing opticians from a family business, with a loyal clientele and a collective registration system. Progression rates in this cohort were in line with other European studies, suggesting that our results are generalizable to the European population at large.[8, 17, 19-21]

Potential limitations of our study should also be mentioned. The design was retrospective and included persons who developed myopiain the time period 1980-2000. Children growing up then may not be representative of children of today, who are likely to perform even more near work and spend less time outdoors. Participants were from an area with a relative low population density; only 37% lived in an urban environment.[18] Nevertheless, this did not lead to lower progression rates than other studies in European children. Important risk factors such as outdoor exposure and near activities were not assessed in the study. This was a limitation because of the retrospective study design and could explain why children with mild myopia at age 10 still developed high myopia. Unfortunately, this cannot be explained by this study due to the lack of data on these and other risk factors for myopia progression. Another drawback is the classification of first prescription of ≤ -0.5D to -3.0D instead of a variable onset of myopia which may have led to misclassification of persons to an older group.

Persons with a first myopic prescription before the age of 10 years developed a median SER of -4.48D (IQR: -5.37 to -3.42) at adult age. In the American Correction of Myopia Evaluation Trial (COMET study) carried out during the turn of the century, white children with a myopia onset at 6-11 years showed mean SER of -5.04D (SD 0.14) at stabilisation.[8] Our median annual progression in children younger than 10 years (SER -0.45D; IQR: -0.69 to -0.20) and from 10-12 (-0.38D; IQR: -0.54 to -0.19) corresponded well with the mean three year progression rate in the 8-12 year control group of the MiSight Lenses study (-1.24D, SD 0.61 in 3 years), with the 7 year old participants of an Australian cohort (-0.41D) but was slightly more than the 3 year progression rate in the 6-7 to 9-10 year old white European children in the Northern Ireland Childhood Errors of Refraction (NICER) Study (-1.14D, 95%CI -3.13 to -0.63).[19, 20, 22] Our rate in children aged 13-15 years (-0.19D, IQR -0.08 to -0.33) was slightly more than the mean three year progression rate in children from the NICER study (-0.33D, 95%CI, -1.63 to 0.63) but less than the annual rate of 13 year old Australians (-0.31D), though 47.3% of these children was of non-western background.[20, 22] Our rate appeared somewhat lower than the progression in 6-15-year-old children of the 2-year low dose atropine study from Los Angeles (-1.2D; SD 0.7 in 2 years), but this retrospective study included mainly children from Asian ethnicity.[21] Other Asian studies also reported higher rates (-0.8D/year).[23] Progression of myopia decelerated with age in our study to -0.05D (IQR: -0.13 to 0.0) in those aged 19-21 years, which was slightly less compared with the progression found in the mean annual progression by the NICER study (-0.09, 95%CI, -0.51 to +0.19) in children 12-20 years.[24] Higher degrees of adult myopia showed faster progression, especially before the age of 13. (figure 4) These age patterns confirm observations from others who also found the steepest progression patterns in the youngest age group.[8, 17, 20, 25-27]

High myopia is clinically the most significant outcome of myopia. Our time-to-event curves provide insight for development of this refractive error category as a function of age. (figure 5) All persons with SER -3D at 10 years developed high myopia by adult age. We think this degree of refractive error developed in the first decade can serve as an indicator for professionals to maximise myopia control and lifestyle advice to reduce final refractive error. Unfortunately, lower refractive errors at age 10 did not exclude development of high myopia; hence, all children with a first myopic prescription below 10 years of age should be followed with care.

Similar to the children in the COMET Trial, gender was not associated with the final degree of myopia. Asian studies did find predilection for females, girls had both higher mean SER and stronger progression. Although we observed a slight gender difference in progression rate in one age category, this difference was minimum and did not exceed -0.03D per year.[28] Lifestyle seems to be a likely explanation to the findings in Asian girls.

In conclusion, our results provide myopic refractive error trajectories during the entire youth for Europeans and present the risk of high myopia as a function of age and refractive error in childhood. With its practical simplicity, the DREAM study can be used to evaluate myopia progression in white children and may serve as a guide for treatment outcomes in myopia control programmes.

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Supplementaries

Supplementary table 1: number of subjects in the analysis

Total sample n = 2555*	
Progression	
Under 10 years to 10-12 years	N = 253
10-12 to 13-15 years	N = 562
13-15 to 16-18 years	N = 729
16-18 to 19-21 years	N = 882
19-21 to 22-25 years	N = 1270
First myopic prescription and measurement at 22-25 years	N = 946
Under 10 years to 22-25 years	N = 92
10-12 to 22-25 years	N = 115
13-15 to 22-25 years	N = 133
16-18 to 22-25 years	N = 117
19-21 to 22-25 years	N = 489
Cumulative risk high myopia	
Under 10 years	N = 279
10-12 years	N = 751
13-15 years	N = 1083

* Two orders of myopic eyeglasses with an interval of one year or more until the age of 25 years

Supplementary Table 2: Cumulative incidence of high myopia according to spherical equivalent of refraction in diopters per age category.

Age (years)	SER	Subjects (N)	Median survival time (Age, Y [95% CI])	5 years survival	10 years survival
Under 10		*278*			
	≤ -0.5D to ≥ -1.5D	132	NR	95.6 (2.0)	85.8 (3.9)
	< -1.5D to ≥ -3.0D	120	24.9 (NE)	88.8 (3.6)	67.4 (5.4)
	< -3.0D to ≥ -4.5D	23	16.0 (12.9 – 19.0)	49.5 (12.3)	21.2 (10.7)
	< -4.5D to ≥ -6.0D	3	11.2 (10.0 – 12.5)	NR	NR
10 – 12		*751*			
	≤ -0.5D to ≥ -1.5D	285	NR	99.0 (0.7)	97.0 (1.7)
	< -1.5D to ≥ -3.0D	323	NR	96.9 (1.2)	85.8 (3.0)
	< -3.0D to ≥ -4.5D	106	24.4 (21.7 – 27.1)	80.9 (4.2)	55.6 (6.3)
	< -4.5D to ≥ -6.0D	37	16.2 (14.3 – 18.0)	40.7 (8.5)	17.2 (7.3)
13 – 15		*1083*			
	≤ -0.5D to ≥ -1.5D	371	NR	99.0 (1.0)	99.0 (1.0)
	< -1.5D to ≥ -3.0D	446	NR	100 (NE)	88.2 (6.0)
	< -3.0D to ≥ -4.5D	178	NR	94.4 (2.1)	76.8 (8.1)
	< -4.5D to ≥ -6.0D	88	19.9 (18.9 – 20.8)	48.1 (6.1)	7.6 (6.3)

95% CI = 95% confidence interval
NE = not evaluable
NR = not reached

4.1

Effectiveness study of atropine for progressive myopia in Europeans

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Effectiveness study of atropine for progressive myopia in Europeans

ABSTRACT

Purpose: Randomized controlled trials have shown the efficacy of atropine for progressive myopia, and this treatment has become the preferred pattern for this condition in Taiwan. This study explores the effectiveness of atropine 0.5% treatment for progressive high myopia and adherence to therapy in a non-Asian country.

Methods: An effectiveness study was performed in Rotterdam, the Netherlands. Overall 77 children (mean age 10.3 years ±2.3), of European (n = 53), Asian (n = 18) and African (n = 6) descent with progressive myopia were prescribed atropine 0.5% eye drops daily. Both parents and children filled in a questionnaire regarding adverse events and adherence to therapy. A standardized eye examination including cycloplegic refraction and axial length was performed at baseline and 1, 4, and 12 months after initiation of therapy.

Results: Mean spherical equivalent at baseline was -6.6D (± 3.3). The majority (60/77, 78%) of children adhered to atropine treatment for 12 months; 11 of the 17 children who discontinued therapy did so within 1 month after the start of therapy. The most prominent reported adverse events were photophobia (72%), followed by reading problems (38%), and headaches (22%). The progression rate of spherical equivalent before treatment (-1.0D/year ± 0.7) diminished substantially during treatment (-0.1D/year ± 0.7) compared to those who ceased therapy (-0.5D/year ± 0.6; P = 0.03).

Conclusion: Despite the relatively high occurrence of adverse events, our study shows that atropine can be an effective and sustainable treatment for progressive high myopia in Europeans.

INTRODUCTION

Worldwide, the prevalence of myopia has been rising dramatically, and it is estimated that 2.5 billion people will be affected by myopia by 2020.[1] South-East Asia isnow facing a myopia frequency up to 95.5% in young academics[2, 3], but a rising trend has also been observed in recent European studies.[4] The high rise also includes the prevalence of high myopia (< -6D; axial length ≥ 26 mm), which in particular is associated with severe complications such as myopic macular degeneration, retinal detachment, and glaucoma.[2] The absolute risk of severe visual impairment is 30% in individuals with axial length of 26 mm, and increases up to 95% in those with an axial length of 30mm or more.[5, 6]

These dramatic figures create the need for effective counteractions. Current treatment options for progressive myopia can be categorized in conservative and pharmacological interventions.[7] The effects of the conservative regimens, except for the orthokeratology, are relatively small.[8] Pharmacological intervention has a much higher efficacy, in particular treatment with topically applied atropine eye drops.[9]

Atropine, a non-selective muscarinic receptor antagonist (M-antagonist), is the most studied pharmacological agent for the intervention of progressive myopia.[10] In animals, topical atropine showed an inhibitory effect on lens-induced and deprived myopia.[11] In humans, the use of atropine to reduce myopic progression was published decades ago,[12] but it was not until the ATOM study performed their large randomized clinical trial in 400 children of Asian ethnicity that atropine was acknowledged as an effective treatment for myopia progression.[10] This 2-year study found 75% reduction of myopic progression with atropine 1%, and did not report serious side effects. A systematic Cochrane review on atropine studies reported that myopia progression can be reduced by 0.80 to 1.0D after a year of treatment of atropine 0.5 and 1%, respectively.[7]

Atropine is the preferred practice pattern for progressive myopia in Taiwan.[13] As early as the year 2000, the Ophthalmological Society of Taiwan advised to use atropine to slow down myopia progression.[13] This treatment is prescribed to nearly 50% of Taiwanese children with progressive myopia.[13] Although opical use of atropine is known to cause photophobia and accommodation lag, these adverse events do not appear to hamper its implementation in Taiwanese children. By contrast, the lighter iris color in Europeans is generally considered as a barrier for its use in the Western world.[14] Moreover, some studies have suggested that atropine is less effective in persons of non-Asian descent.[15]

The aim of this study was to investigate the effect of atropine for progressive myopia under 'real-world' conditions in a non-Asian country. We compared rates of myopia progression in consecutive children before and after therapy, assessed common complaints, evaluated reasons for discontinuation, and developed practice guidelines.

METHODS

Study design, population and intervention

The design was an effectiveness study, and was prospective and clinic-based. The setting was Erasmus Medical Center and Sophia Children's Hospital in Rotterdam, the Netherlands, and all consecutive children younger than 18 years of age presenting with progressive myopia were eligible for the study. Inclusion criteria were spherical equivalent (SE) ≤ -3D and SE progression rate ≥ 1D/year under cycloplegic conditions; exclusion criteria were myopia related to retinal dystrophies or collagen syndromes, and developmental disorders. Eligible children and parents received a patient information leaflet followed by oral consultation. After providing written informed parental consent (parents or legal guardians for children ≤ 12 years; also including children for ages 12+ years), participants received a prescription of atropine eye drops 0.5% (FNA Dutch pharmacists). Both eyes were treated by atropine eye drops once daily before bedtime by the parent. The study and protocol adhered to the tenets of the Declaration of Helsinki, and were approved by the Medical Ethics Committee of the Erasmus Medical Centre.

Eye examination

A standardized ophthalmological examination was performed at baseline, 1 month, 4 months, and 12 months after initiation of atropine treatment. Best corrected visual acuity was performed with a decimal equivalent (minutes) visual acuity chart at 6 m distance. Binocular reading visual acuity was performed with the LogMAR-based Dutch Radner reading chart at 25 or 40 cm.[16] Pupil size was measured with Richmond Products Clear Pupilometer (Albuquerque, NM, USA). At baseline, full cycloplegia was obtained 45 min after administration of 1% cyclopentolate eye drops. At follow up, cycloplegia was already present at examination due to the use of atropine; this was confirmed by the investigators with dynamic retinoscopy, and was therefore considered a measure of compliance. Subsequently, the refractive error was measured with a Topcon auto refractor KR8900 (Topcon, Tokyo, Japan); in younger children with a Nikon Retinomax 2 auto refractor (Nikon, Tokyo, Japan), and in very young or uncooperative children refractive error was determined by an experienced orthoptist (JRP) performing retinoscopy with a Heine beta 200 retinoscope (Heine Optotechnik, Herrsching, Germany) and lenses according to standard protocols. The same devices were used throughout the study period. Spherical equivalent was calculated using the standard formula. (SE = sphere + 1/2 cylinder). Axial length was measured with the IOL Master 500 (Carl Zeiss MEDITEC IOL-master, Jena, Germany) at each visit.

Risk factors and adverse events

At baseline, and after 4 and 12 months after the start of atropine, as well as 1 month after cessation of therapy, parents and children filled in a questionnaire evaluating adverse events. The questionnaires were filled in independent of each other at different locations; children < 8 years of age received help of the investigator. The questions for the parents concerned risk factors for myopia, adverse events, and adherence to therapy; the questions for the children concerned only the latter two, and were simplified versions of the same questions for parents.

Statistical analysis

All data were entered into a database as nominal or ordinal variables. Proportions were calculated, and data before and after start of atropine treatment were compared with Fisher's exact test. Biometric measures of the eye were analyzed using Mann-Whitney U non parametric test. Throughout the study, P = 0.05 was used as border of significance.

The annual progression rate before treatment was calculated by subtracting the SE at baseline from the SE estimated 1 year before treatment for each participant. We calculated the progression rate during treatment by subtracting the SE at one year follow up (-6.8D ± 3.6) from the SE estimated at baseline (-6.7D ± 3.6).The rate was analyzed with Wilcox on signed ranks test to identify short term differences during the 1 year of treatment.

Risk of adverse events and adherence to therapy were estimated using logistic and linear regression analysis. Multivariate logistic regression analysis was used to determine the risk of discontinuation of therapy with age, gender, baseline SE, and ethnicity in the model. All statistical tests were performed by using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

From March 2011 to July 2013, a total of 84 consecutive progressive myopic children visited our clinic and were considered eligible for this study. Of these, 78 (92.9%) consented to participation and 6 (7.1%) refused. Of those consented, 1 (1.3%) child was lost to follow-up during the course of the study. The remaining 77 children completed 12 months of follow up.

Demographics of the study population are summarized in Table 1. Gender was evenly distributed; the mean age was 10.3 (± 3.2) years, and two thirds of the children had European ancestry. The mean refractive error 1.1 (± 0.6) year before treatment was -5.6D (± 3.9). At baseline, mean refractive error was -6.63D (± 3.31), resulting in a mean progression rate of -1.0 (0.7). Half (50.6%) of the children were already highly myopic (SE > -6D, ranging from -6.13D to -18.63D). Mean pupil diameter before treatment was 4.4mm (95% CI, 3.3-5.5). The majority (84.7%) reported at least one myopic parent. Five children had been adopted, and had no information on the refractive error of the biological parents.

Table 1: Distribution of demographics and clinical measures of study participants with progressive myopia

Patients, n		77
Gender, n (%)	male	39/77 (50.6%)
	female	38/77 (49.4%)
Mean age in years (SD), (range)		10.34 (± 3.21) (2.7 to 16.8)
Mean SE in D (SD)		-6.63 (±3,31)
Mean age in groups, n (%)	< 9 yrs	26/77 (33.8%)
	9 - 11 yrs	48/77 (32.5%)
	12 - 16 yrs	22/77 (33.8%)
Ethnicity §	European	53/77 (68.8%)
	Asian	18/77 (23.4%)
	African	6/77 (7.8%)
Age started reading § *, n (%)	< 5 yrs	26/72 (33.8%)
	5 yrs	20/72 (26.0%)
	6 yrs	20/72 (26.0%)
	> 7 yrs	4/72 (5.2%)
	never	5/70 (7.1%)
Reading habits § **,n (%)		
	<5 h/wk	33/70 (42.9%)
	5-15 h/wk	23/70 (29.9%)
	>15 h/wk	7/70 (9.1%)
Outdoor activities §, n (%)	<1 h/day	23/77 (29.9%)
	1-3 h/day	45/77 (58.4%)
	>3 h/day	9/77 (11.7%)
Parental presence of myopia, n** (%)		57/77 (74.0%)

§ Obtained by questionnaire
* Only current readers could be included for this question
** Parents of 7 children were not able to answer this question: n=5 no reading skills, n=2 insufficient reading skills (at time of questionnaire).

Of the 77 children, 60 (78%) adhered to therapy for the complete follow-up of 1 year. Annual progression rates showed an advantage for the children who stayed on therapy (0.1D/year) versus the children who discontinued therapy (0.5D / year) (P = 0.03). (Table 2).

Mean change in SE from baseline to 1 year before and during the year of treatment is presented in Figure 1. The SE difference from baseline to the first month of treatment appeared to improve by 0.19D (± 0.41) compared to baseline, but this temporary inverse progression of myopia was not sustained thereafter. The SE difference from baseline to 6 and 12 months was significantly lower than before therapy and approached almost zero (0.12 and -0.05D, P < 0.01).

Table 2 Spherical equivalent and axial length over time in children who prolonged and ceased atropine therapy

	Prolonged therapy N=60 (77.9%)	Ceased therapy N=17 (22.1%)	P value
Age (yr) at baseline study, mean (±)	10.0 (3.2)	11.4 (2.8)	0.09
Spherical Equivalent (SE)	**SE (D)**	**SE (D)**	
12 months prior to treatment	-5.6 (3.9)	-5.7 (3.1)	0.85
Start treatment	-6.7 (3.6)	-6.5 (2.8)	0.80
12 months after start treatment	-6.8 (3.6)	-7.1 (2.6)	0.55
Annual myopic progression rate (PR)			
Pre- treatment to start treatment (D/year)	-1.0 (0.7)	-0.9 (0.5)	0.33
12 months after start treatment (D/year)	-0.1 (0.7)	-0.5 (0.6)	**0.03**
Axial Length (AL)			
Start treatment (mm)	25.19 (0.97)	25.46 (1.21)	0.82
12 months after start treatment (mm)	25.54 (1.35)	25.83 (1.4)	0.66
Annual AL progression rate (PR)			
Pre- treatment to start treatment (mm/year)	n.a.	n.a.	
12 months after start treatment (mm/year)	-0.11 (0.20)	-0.12 (0.14)	0.73

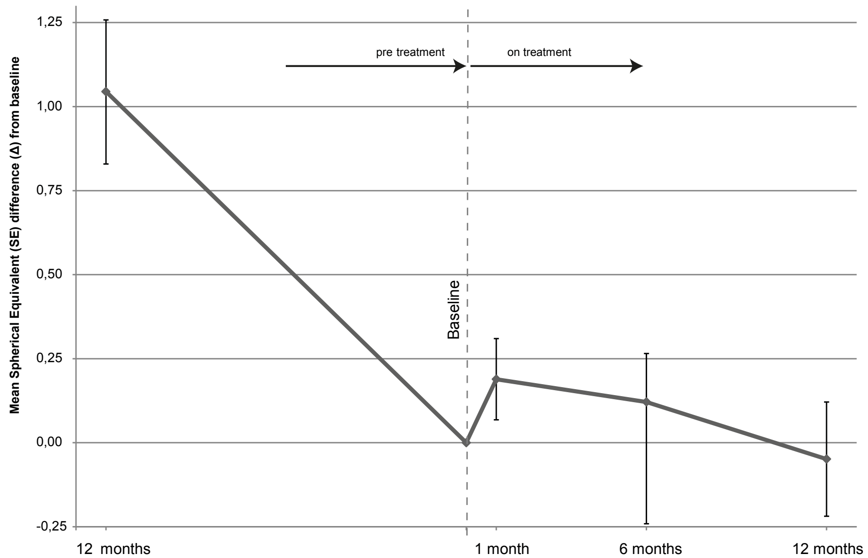

Figure 1 Mean change in spherical equivalent from baseline one year before and during the year of treatment. Error Bars present 95% CI.

Table 3 Adherence to atropine therapy and time and reasons for ceasing

		parent report	child report
maintained therapy		60/77 (77.9%)	60/77 (77.9%)
adherence			
	full adherence	39/60 (65.0%)	36/60 (60%)
	adherence >6x /wk	17/60 (28.3%)	18/60 (30%)
	adherence 4-6x /wk	3/60 (5.0%)	5/60 (8.3%)
	adherence <4x /wk	1/60 (1.7%)	1/60 (1.7%)
reason non-adherence			
	forgotten	37/60 (61.7%)	28/60 (46.7%)
	adverse events	2/60 (3.3%)	3/60 (5%)
	application eye drops	1/60 (1.7%)	2/60 (3.3%)
Ceased therapy		17/77 (22.1%)	17/77 (22.1%)
duration of therapy before ceasing	<1 wk	7/17 (41.2%)	7/17 (41.2%)
	1-4 wk	4/17 (23.5%)	4/17 (23.5%)
	>4 wk	6/17 (35.3%)	6/17 (35.3%)
reason for ceasing			
	adverse events	14/17 (82.4%)	14/17 (82.4%)
	application eye drops*	1/17 (5.9%)	1/17 (5.9%)
	other	2/17 (11.8%)	2/17 (11.8%)

Age modified the treatment effect significantly (P = 0.01): children younger than 9 years of age had the lowest treatment effect (annual progression rate -0.49D, CI, -0.90 to -0.08); 9-12 year-olds had more effect (annual progression rate -0.06D, CI, -0.47 to +0.35), and older children had the highest treatment effect (annual progression rate 0.02D, CI -0.27 to +0.3). Ethnicity (P = 0.58) nor gender (P = 0.76) significantly influenced annual progression rate during treatment.

More than half (36/60; 60%) of the children who adhered to therapy did not report any skips in therapy administration. None showed more than 0.5 D accommodation on dynamic retinoscopy. The mean pupil diameter was 7.0 mm (± 0.63) during the follow up visits. The most frequent reason for skips was forget fulness. Overall 61.7% of children who commenced with atropine, 17 stopped treatment, of whom 11 (64.7%) within the first 4 weeks. (Table 3) Adverse events were reported as the primary reason (82.4%). The frequency of dropouts was higher in those aged 12 years and over (13.0% in age < 12 years vs 44.4% in 12+ years; P < 0.01).

Table 4 Adverse events in children who maintained and ceased therapy

	Maintained therapy, *n* (%)		Ceased ** therapy, *n* (%)	
	Parent report	*Child report*	*Parent report*	*Child report*
no	11/60 (18.3%)	11/60 (18.3%)	2/16 (12.5%)	2/16 (12.5%)
photophobia	36/60 (60%)	42/60 (70.0%)	12/16 (75.0%)	13/16 (81.2%)
reading problems *§	13/54 (24.1%)	14/54 (25.9%)	12/15 (80.0%)	12/15 (80.0%)
headache	4/60 (6.7%)	13/60 (21.7%)	5/16 (31.2%)	4/16 (25.0%)
systemic (flushes)	2/60 (3.3%)	2/60 (3.3%)	1/16 (6.2%)	1/16 (6.2%)
infections (conjunctivitis, blepharitis)	2/60 (3.3%)	1/60 (1.7%)	0/16 (0%)	0/16 (0%)
other	6/60 (10.0%)	4/60 (6.7%)	2/16 (12.5%)	3/16 (18.8%)

* Only in children who started to read, n= 54 vs. n=15,
** 16/17 could be included, only 1 participant did not return the questionnaire
§ Significant difference (P=<0,01) between those who maintained therapy and those who did not

The questionnaires addressing treatment response and adverse events showed remarkable similarity between parents and their children, although children reported complaints at slightly higher frequencies. Adverse events occurred often, 63 (82.9%) reported these by both parents and children. Photophobia (72.4%) and reading problems (37.7%) were reported most frequently; 22.4% reported headaches; and systemic flushes occurred only in a minority. Those who discontinued therapy reported reading problems significantly more often than those who maintained therapy (12/15 (80%) vs 13/54 (24.1%), P <0.01). (Table 4) Other reported events were rare: pain in the eye, irritated eyes, overflow of tears, trouble with depth perception, cosmetically disfiguring pupils and an unpleasant taste in mouth (all reported only in one patient).

DISCUSSION

Our study shows that atropine 0.5% can be an effective treatment for progressive myopia in a European setting. The mean progression rate before the year of intervention was -1.0D (± 0.7)/year. Atropine 0.5% reduced this to -0.1D (± 0.7)/year during treatment. Despite a high frequency of adverse events, most children managed to prolong therapy for the entire study period. Those children who prolonged therapy had a significant advantage over those who stopped (P = 0.03). The effect of treatment was dependent on age, and was most prominent in teenagers. Although not powered to test for ethnicity and gender, these did not appear to influence treatment outcome in our study.

We deliberately chose a pragmatic study design to make a translation from findings of efficacy studies to daily practice. Numerous studies including randomized controlled trials have reported on the efficacy of atropine treatment for progressive myopia.

An effectiveness study such as ours more closely reflects daily practice as it consisted of a heterogeneous patient population with a large range in refractive errors and age, and inclusion of multiple ethnicities. Other strengths of our study are the standardized measurements of cycloplegic refraction, and the cross evaluation of parents and children by questionnaire to improve the validity of data on adherence and adverse events. Among the limitations are the relatively short follow up, and the absence of a flexible dosing regimen which would have allowed tailored therapy for each subject.

Higher concentration atropine eye drops are known for their frequent occurrence of adverse events, and our study confirms this. Most commonly reported adverse events were photophobia and reading problems. Headaches occurred in approximately one fifth of the patients, but were reported to be mild and transient. Flushes of the cheeks were observed in only three children, but were not a reason to discontinue therapy.

Cessation of therapy most often occurred shortly after the start of therapy. Children who managed to adhere to therapy for 4 weeks were more likely to prolong therapy thereafter. Most important startup difficulties were adaptation to the bright light and coping with reading problems. Following from this observation, we therefore recommend to prescribe transitional multifocal glasses at the initiation of therapy. We also experienced that comprehensive instruction of the parent and child through information brochures and oral clarification was greatly appreciated, and may improve motivation. After cessation of therapy, a rebound, or catch-up, growth spurt has been described.[17] Tong et al. found that the positive effect of atropine lasted up to three years before being caught up by the rebound effect.[18] Maintaining therapy for a longer period of time and tapering with lower concentrations after achieving stability are suggested to prevent this rebound effect.[19]

Atropine is the standard of care for myopia progression in Taiwan.[13] The reasons for not prescribing atropine for progressive myopia in western countries is as yet unclear. One reason may be the report of a higher efficacy of treatment in Asians than in Europeans. Although our power to study differences herein was low, our study could not confirm any differences between ethnicities. Another reason may be fear for serious and irreversible complications after prolonged use, but this is not substantiated by literature. Long term effects of atropine treatment have been investigated in both animal as well as human studies, and[20, 21] photochemical damage to the retina due to enlarged pupil for a longer period of time under daylight conditions has not been reported.[22, 23] Therefore, daily atropine appears to be a safe treatment, even if used for several years.[12, 24, 25]

A remarkable finding was that the refractive error showed a hyperopic shift after 4 weeks which disappeared after 4 months. This effect could be caused by the stronger cycloplegic effect of atropine over classical cycloplegic agents used in the clinic, such as cyclogyl.[26] The reduction in refractive error could also be the result of a temporary thickening of the choroid, a phenomenon observed in animal studies.[27]

How atropine manages to interfere with myopia progression has not been well established, neither is there agreement on the site of action.[28] This may be the retina, because amacrine cell scan express muscarinic receptors on their cell membrane.[29] Binding of atropine to the muscarinic receptors of amacrine cells has been hypothesized to increase the release of dopamine, which fits well with the view that dopamine is an inhibitory chemical mediator for eye growth.[30] Reduction of ɣ-aminobutyric acid (GABA) levels is also a possible mechanism, since this neurotransmitter was shown to be down regulated following atropine treatment in myopia induced mice.[31] Other explanations include an effect of atropine via the sclera. Scleral fibroblast cells carry all 5 muscarinic receptors on their cell membrane and binding to atropine may interfere with scleral remodeling.[32] The inhibitory effect of atropine is not likely executed through an accommodative mechanism, because the inhibitory effect of atropine on eye growth is also observed in chicks, and these animals activate the ciliary muscle via nicotine receptors rather than the muscarinic receptor.[30]

Taken our findings together with the existing literature, we suggest the following guidelines for doctors treating myopes at risk for high myopia in everyday clinical practice: first, identify and discuss the risk profile of the patient and provide lifestyle advice such as increase of the time spent outdoors. Second, start intervention with atropine 0.5% and prescribe transitional multifocal glasses. Third, perform regular follow up examinations including visual acuity, reading acuity, cycloplegic refraction and axial length. Fourth, adjust treatment regimen. In contrast, when SE and axial length have remained stable for a period of 12 months, gradually taper the atropine concentration to naught.

In conclusion, our study provides external validity of findings from randomized controlled trials and shows that atropine can be effective for progressive myopia in daily clinical practice. Atropine should be considered a treatment option in children at risk of high myopia anywhere in the world.

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4.2

A three year follow-up study of atropine treatment for progressive myopia in Europeans

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A three year follow-up study of atropine treatment for progressive myopia in Europeans

ABSTRACT

Background: Atropine is the most powerful treatment for progressive myopia in childhood. This study explores the 3-year effectiveness of atropine in a clinical setting.

Methods: In this prospective clinical effectiveness study, children with progressive myopia ≥ 1D/year or myopia ≤ -2.5D were prescribed atropine 0.5%. Examination, including cycloplegic refraction and axial length (AL), was performed at baseline, and follow-up. Outcome measures were spherical equivalent (SER) and AL; annual progression of SER on treatment was compared with that prior to treatment. Adjustments to the dose were made after 1 year in case of low (AL ≥ 0.3mm/year) or high response (AL < 0.1mm/year) of AL.

Results: A total of 124 patients were enrolled in the study (median age 9.5, range 5-16 years). At baseline, median SER was -5.03D (interquartile range (IQR): 3.08); median AL was 25.14mm (IQR 1.30). N = 89 (71.8%) children were persistent to therapy throughout the three year follow-up. Median annual progression of SER for these children was -0.25D (IQR 0.44); of AL 0.11mm (IQR 0.18). Of these, N = 32 (36.0%) had insufficient response and were assigned to atropine 1%; N = 26 (29.2%) showed good response and underwent tapering in dose. Rebound of AL progression was not observed. Of the children who ceased therapy, N = 9 were lost to follow-up; N=9 developed an allergic reaction; and N = 17 (19.1%) stopped due to adverse events.

Conclusion: In children with or at risk of developing high myopia, a starting dose of atropine 0.5% was associated with decreased progression in European children during a 3 year treatment regimen. Our study supports high-dose atropine as a treatment option for children at risk of developing high myopia in adulthood.

INTRODUCTION

The prevalence of myopia is increasing all over the world, and has reached the highest frequencies in young adults in South Korea (96.5%), but has also increased significantly in Europe (49.2%).[1, 2] The trait is determined by several optical components, of which increased axial length (AL) is the most important.[3] High myopia, i.e. refractive errors -6D or more, has increased from 4.2 to 21.6% in East-Asians and from 1.4 to 5.3% in Europeans.[2, 4] Countries which presently have a low prevalence will follow these trends, as myopia prevalence is driven by lifestyle changes such as less time outdoors and increased near work activities.[5] Myopia carries a significant risk of retinal detachment, glaucoma, and myopic macular degeneration, which is most prominent for severe refractive errors.[6] Of those with high myopia, one in three develops bilateral severe visual impairment or blindness with age.[7] This highlights the need for myopia control strategies in children with progressive myopia, in particular progression to high myopia.[5, 8, 9]

During the last 10 years, many intervention studies for myopia progression have emerged.[10-12] Although life-style adjustments and optical solutions can be effective, pharmacological interventions targeting muscarinic receptors have shown the highest efficacy on reduction of eye growth.[13, 14] Atropine is a nonselective muscarinic receptor antagonist which has been tested for progressive myopia in several dosages.[10] High dosages, 0.5% and 1%, are the most effective in reducing eye growth, but have drawbacks as pupil dilatation, loss of accommodation and potential rebound of spherical equivalent of refraction (SER) after stopping.[15] The lowest dose of atropine, 0.01%, has become popular because it has minimal side effects and virtually no rebound after stopping, but reduction on AL progression is also minimal.[16-18]

In an earlier study, we reported 1 year results of intervention with atropine 0.5% for progressive myopia in a clinical setting in Europe. In children with already severe myopic refractive errors (mean SER, -6.6D) and progression of myopia 1D / year or more, we showed that atropine 0.5% reduced myopia progression to 0.1D / year. Despite the side effects, persistence to therapy was 78%.[19] We extended this study, and now report 3 year follow up after the starting dose of atropine 0.5%. We addressed the photophobia and accommodation problems by prescribing photochromic multifocal spectacles.

MATERIALS AND METHODS

Study design and population

The design was a prospective clinic-based effectiveness study. The setting was a single center study in the Erasmus Medical Center in Rotterdam, the Netherlands, which included the Sophia Children's hospital. Erasmus Medical Center has been a referral center for myopia control since 2010. Two examiners (JRP and AS) obtained cycloplegic refractive error and AL in the children throughout the study. Inclusion criteria have been described previously.[19] In short, consecutive children 5-16 years presenting with SER progression rate of at least 1D / year, or an SER of at least -2.5D in children 10 years and younger, or SER -5.0D in children aged 11 years or older were eligible. Exclusion criteria included those with pediatric pathology (e.g., amblyopia, strabismus or systemic disorders) and low vision due to retinal dystrophies. The current report included children who presented at our clinic between March 2011 and January 2015. Children and parents received a patient information leaflet followed by oral consultation, and participants provided written informed parental consent (parents or legal guardians and children when age 12+ years; only parents and legal guardians when age < 12 years). All patients were scheduled for follow-up visits every 6 months from baseline onwards. The occurrence of serious adverse events was noted in the medical chart, and affected patients were referred to a specialist. The study adhered to the tenets of the

Declaration of Helsinki, and was approved by the Institutional Review Board of the Erasmus Medical Center.

Intervention

The intervention at baseline was atropine eye drops 0.5%; both eyes were treated before bedtime. After at least 1 year of atropine 0.5%, adjustments to the dose were made in case of insufficient response or stability of SER and AL. Insufficient response was considered present when myopia progressed ≥ -1 D / year, and AL increased ≥ 0.3 mm/year. Moderate response was defined as SER ≥ -0.5D /year to -1 D / year and AL ≥ 0.2 mm / year to 0.3 mm / year; and good response as SER <- 0.5 D / year and AL < 0.2 mm / year.[15] In children with good response, atropine concentration was tapered to 0.25%, and further to 0.1% and 0.01% every 6 months when myopia progression remained stable. Increase of atropine concentration was indicated if the progression was moderate to insufficient. All dosages were distributed in multi dose bottles preserved with benzalkonium chloride, sodium edetate, boric acid and purified water (FNA Dutch pharmacists).

Eye examination

A standardized ophthalmological examination was performed at baseline, and at 6, 18, 24, 30, and 36 months. Baseline and follow up measurements included a cycloplegic refractive error measurement with two drops of cyclopentolate 1% with 5 min interval and a minimum waiting time of 45 min after the first drop. In very dark irises with pupil diameter < 6mm an additional drop op cyclopentolate was adjusted. In case of atropine 0.5% and 1% interventions, cycloplegia was considered already present. Refractive error was measured by using a Topcon auto refractor (KR8900). At least 3 measurements per eye were averaged to the mean refractive error per eye. SER was calculated as the average sphere + 1/2 cylinder of both eyes. AL was measured with the IOL Master (Carl Zeiss MEDITEC IOL Master 500, Jena, Germany) and for AL five measurements per eye were averaged to a mean AL. The average AL of both eyes was used for the analysis. Best-corrected Snellen visual acuity was performed at 6 m distance with a decimal equivalent. The LogMAR based Dutch Radner chart was used to assess binocular reading visual acuity at 25 or 40 cm. To assess compliance with atropine eye drops, dynamic retinoscopy was performed according standard protocol to detect presence of accommodation paralysis and the Richmond Products Clear Pupilometer was used to measure pupil size (Albuquerque, NM, USA).

Statistical analysis

Primary outcome was the annual progression rate of SER and AL for years 1-3. The pretreatment progression rate of SER was calculated using cycloplegic refractive error measurements obtained from medical records. Both SER and AL showed a skewed distribution, therefore medians were calculated as well as the inter quartile range (IQR). Differences in outcomes between the various dosing regimens, and between prolongation and cessation of therapy were assessed with Mann-Whitney U nonparametric test for continuous outcome measures, and with Fisher's exact test for categorical outcome measures. Differences in progression rates in SER and AL were obtained with Wilcoxon signed rank test. Correlation between annual progression of SER and AL was calculated with Pearson's regression analysis. Throughout the study, $p < 0.05$ was used as criterion of statistical significance. All statistical tests were performed by using IBM SPSS Statistics for Windows, Version 24.0. (IBM Corp. , Armonk, NY, USA).

RESULTS

The current analysis included 124 children who started atropine 0.5% treatment for progressive myopia. Informed consent was obtained from all parents of children and all children aged 12 years or older.

Demographics of the study population are summarized in Table 1. Gender was evenly distributed and the median age was 9.5 years (IQR: 4). The majority of children (66.9%) had European ethnicity. Median SER 1 year prior to the study was -3.88D (IQR: 4.00). At baseline, median SER was -5.03D (IQR: 3.08) demonstrating an annual progression rate of SER of more than 1D prior to treatment. High myopia (SER ≤ -6D) was present in 46 (37.1%) of children (range -6.13 to -17.06D); median AL was 25.14 (IQR: 1.30). Parental myopia was reported by 80.6%; high parental myopia by 37.9%.

Table 1 Distribution of demographics and clinical measures of children eligible for three year follow up data using atropine 0.5% for progressive myopia

Characteristics at baseline		
Patients, n		124
Gender, n (%)	Female	67/124 (54%)
Median age in years (IQR)		9.5 (4)
Ethnicity [a]	European	83/124 (66.9%)
	East Asian	13/124 (10.5%)
	Other [b]	29/124 (22.6%)
Parental presence of myopia, n (%)	No myopia	12/124 (9.7%)
	One parent	51/124 (41.1%)
	Both parents	49/124 (39.5%)
	Missing [c]	12/124 (9.7%)
Parental presence of high myopia (≤ -6D), n (%)		47/124 (37.9%)
Median onset of myopia in years (IQR)		6 (3)
Median SE in D (IQR)		-5.03 (IQR 3.08)
Median AL in mm (IQR)		25.14 (IQR 1.30)

a. Obtained by medical record
b. Other ethnicities included children with a background form Surinam, Venezuela, the Dutch Antilles, Indonesia and Pakistan.
c. Complete data could not be obtained due to adoption or one parent situation

Results of outcome and adherence are shown in Table 2. Of the 124 children, 89 (71.8%) stayed on treatment during the full 3 years of follow up, of these, 31 (34.8%) stayed on 0.5% atropine, 32 (36.0%) increased in dose to 1%, and 26 (29.2%) children decreased in dose. Decreasing the dose did not lead to rebound growth of AL. Of those who ceased therapy, 9 (6.8%) children stopped due to an allergic reaction following the eye drops; 17 (13.6%) children stopped due to photophobia and non-eye-related adverse events; and 9 (6.8%) were lost to follow-up. The 17 children who ceased therapy due to adverse events did so primarily during the first 3 months of treatment. Risk factors for non-adherence were not significant although children who ceased therapy were somewhat older.

In those who fulfilled 3 years of treatment, the median annual progression of SER was -0.25D (IQR: 0.44); of AL 0.11mm (IQR: 0.18).

Figure 1 represents the median annual progression rate of SER. Median progression was reduced to 0.00D in the 1st year, and -0.41D and -0.38D in the 2nd and 3rd year (all $p < 0.01$).Comparing these progressions to those prior to treatment, annual reduction rates of SER were 100, 65, and 68.2.% (all $p < 0.01$; Fig.1).

The correlation between SER and AL measured during the study was strong with Pearson's R 0.82 ($p < 0.01$). Annual progression of AL was 0.04 mm in the 1st year, and 0.16 mm and 0.14 mm in the 2nd and 3rd, respectively. (Fig. 2) We could not compare these progressions with those prior to treatment, as AL had not been measured by the referring clinics 1 year prior to treatment.

With respect to treatment response, 76% of children stayed stabilized within -0.5D of SER progression during the 1st year; and 53 and 61% in the 2nd and 3rd year, respectively (Fig. 3a). AL progression in the 1st year stayed within 0.2 mm in 76%; in the 2nd year in 61%, and in the 3rd year in 74% (Fig. 3b).

Table 2 Median age, spherical equivalent and axial length for different treatment modifications over a 3 year time period in children initially started with atropine therapy 0.5%

	Prolonged therapy N=89 (71.8%)			Ceased therapy N=35 (28.2%)		
	Increased dose N=32	Decreased dose N=26	Same dose N= 31	Allergy stop N=9	Adverse events [b] N=17	Lost to follow up N=9
Median age (year) myopia onset (IQR)	6.0 (3)	7.0 (4)	6.0 (4)	6.0 (5)	6.0 (5)	7.0 (6)
Median age (year) at baseline (IQR)	8.5 (3)	11.0 (4)	9.0 (3)	9.0 (4)	11.0 (5)	12.0 (6)
Median Spherical Equivalent (SE) in D						
One year prior to treatment	-4.5 (4.9)	-2.9 (3.9)	-3.8 (3.1)	-3.6 (6.4)	-4.3 (4.5)	-4.8 (4.1)
Start treatment	-5.8 (3.5)	-4.4 (2.8)	-4.9 (2.8)	-5.4 (4.9)	-5.3 (4.0)	-5.4 (3.0)
First year after start treatment	-6.0 (3.6)	-4.2 (3.5)	-4.8 (2.5)	-7.5 (6.7)	-5.6 (3.7)	n.a.
Second year after start treatment	-6.9 (4.7)	-4.6 (2.8)	-5.2 (2.6)	-8.0 (5.5)	-6.8 (3.3)	n.a.
Third year after start treatment	-7.5 (5.2)	-4.8 (2.6)	-5.6 (2.6)	-8.1 (6.0)	-7.8 (3.7)	n.a.
Median progression rate of SE in D						
One year before treatment (D/year)	-1.0 (1.3)	-1.3 (1.0)	-1.0 (1.2)	-1.1 (2.1)	-0.8 (1.1)	-0.4 (1.0)
First year of treatment (D/year)	-0.4 (0.6)	+0.2 (0.7)	+0.1 (0.5)	-0.4 (0.7)	-0.7 (1.1)	n.a.
Second year of treatment (D/year)	-0.6 (0.7)	-0.3 (0.4)	-0.3 (0.6)	-0.9 (1.3)	-0.8 (0.9)	n.a.
Third year of treatment (D/year)	-0.5 (0.8)	-0.3 (0.3)	-0.3 (0.5)	-0.4 (1.4)	-0.9 (1.1)	n.a.
Median Axial Length (AL) in mm [a]						
Start treatment	25.2 (1.3)	24.7 (1.3)	25.4 (1.6)	25.2 (2.8)	24.8 (1.2)	25.9 (2.5)
First year after start treatment	25.5 (1.7)	24.5 (1.5)	25.3 (1.6)	25.4 (1.5)	25.1 (1.3)	n.a.
Second year after start treatment	25.8 (1.4)	24.7 (1.3)	25.3 (1.6)	n.a.	n.a.	n.a.
Third year after start treatment	25.9 (2.3)	24.8 (1.5)	25.4 (1.5)	n.a.	n.a.	n.a.
Median progression rate AL in mm [a]						
First year of treatment (mm/year)	0.3 (0.2)	0.0 (0.2)	0.0 (0.1)	0.2 (0.3)	0.3 (1.0)	n.a.
Second year of treatment (mm/year)	0.3 (0.3)	0.1 (0.1)	0.1 (0.2)	n.a.	n.a.	n.a.
Third year of treatment (mm/year)	0.2 (0.3)	0.1 (0.1)	0.1 (0.1)	n.a.	n.a.	n.a.

a. AL was not included in the standard ophthalmological examination 1 year prior to start of therapy and was not included in the children who stopped atropine treatment.
b. Adverse events included photophobia, reading difficulties, nightmares, and deterioration of behavioral problems in a child with diagnosis of ADHD.

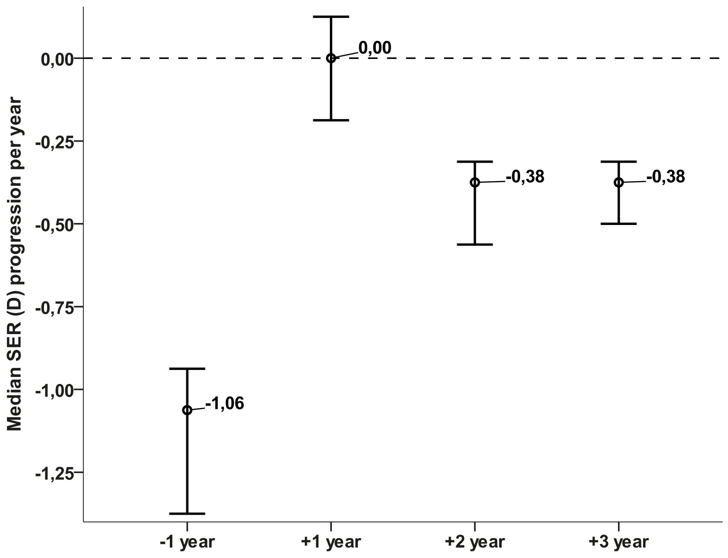

Figure 1: Median Spherical Equivalent (SER) change in dioptres per year in children treated with atropine 0.5% for progressive myopia. Error bars represent the 95% Confidence Interval.

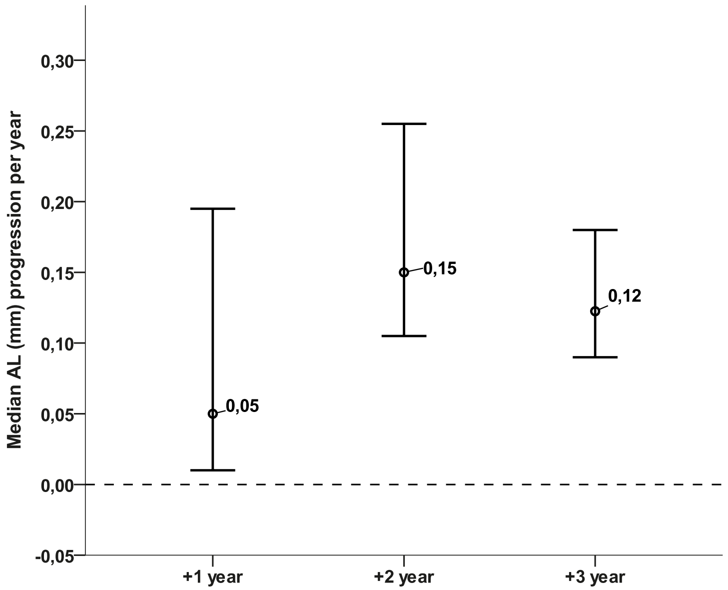

Figure 2: Boxplots represent median Axial Length (mm) change per year in children treated with atropine 0.5% for progressive myopia.

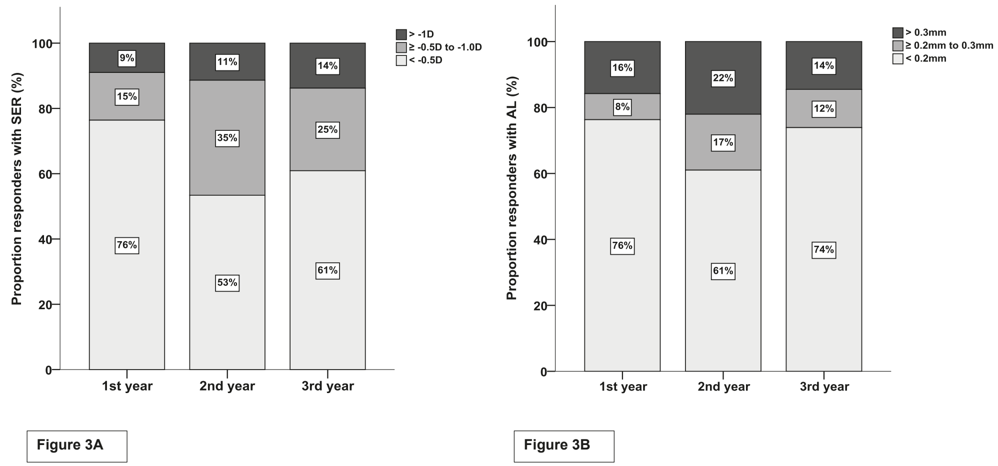

Figure 3: Proportion of good (light gray), moderate (dark gray), and poor (black) responders with respect to spherical equivalent of refraction (a) and axial length (b) in children on therapy for 3 years.

Age was moderately but significantly related to the treatment effect (Pearson's R for SER 0.31, $p < 0.01$; for AL 0.55, $p < 0.01$). Children younger than 10 years of age at the start of therapy had lower treatment effect (median annual progression rate for SER: -0.29D, IQR: 0.44; for AL 0.20, IQR: 0.18) than older children (median annual progression rate for SER: -0.19D, IQR: 0.41; for AL 0.06, IQR: 0.08). None of the other determinants at baseline (SER; ethnicity; gender) were significantly associated with annual progression rate during treatment.

We increased the dose of atropine to 1% in 32/89 (36.0%) children (median progression: -0.69D/year, IQR: 0.72; AL 0.39 mm/year, IQR: 0.19) after a median time of 18 months. This did not diminish progression rates substantially: rates were SER: -0.63D/year (IQR: 0.85) and AL: 0.34mm/year (IQR: 0.30) during the remaining time of the study.

Aside from the photophobia and reading difficulties, other reported adverse events were nightmares by one child and deterioration of behavioral problems in a child with ADHD. No serious adverse events such as tachycardia, acute angle-closure glaucoma, pyloric obstruction, or asthma were reported.

DISCUSSION

This study aimed to investigate the effectiveness of atropine for progressive myopia in a European clinical setting. We treated 124 children who presented with either a high degree of myopia or a high progression rate of SER with atropine eye drops at a starting dose of 0.5%, and followed these children for 3 years. Of these, 89 (71.8%) were persistent with therapy during the total duration of the study period. Median SER progression rates declined to 0.00D in the first year and to -0.41 and -0.38D in the second and third year, respectively. This corresponded well with a median progression rate for AL of 0.04 mm in the 1st year, and 0.16 and 0.14mm in the 2nd and 3rd year, respectively. Despite the slightly lower effect in the 2nd and 3rd year, 61% of children still had < -0.5D of SER progression, and 74% had < 0.2 mm AL elongation during the last year of the study. After the 1st year, 32/89 of patients progressed 0.3 mm or more while on the starting dose, and were switched to atropine 1%. By contrast, 26/89 stabilized to 0.1 mm/year or less, and were allocated to lower dosages. An important determinant of treatment effect was age: those older than 10 years at baseline remained more stable than those younger.

Given the design of this clinical trial, this study has strengths and limitations. We chose to study high dose atropine in a real world setting because randomized controlled trials had already demonstrated ample evidence of safety and efficacy of this treatment.[10, 15, 20-24] Our primary intention was to investigate its implementation in Europeans, and our clinical setting enabled great generalizability of findings. Other merits of the study were the long follow-up period and detailed investigation including cycloplegic refraction and AL. A limitation of our design was the use of pretreatment SER progression rates as a reference rather than a separate control group.[25] It is known that myopia progression rates slow down with age, and this effect may have influenced our findings.[26] In all children who prolonged therapy an initial arrest of the myopia progression was seen in the first year but median progression continued in the second and third year with -0.41D and -0.38D. However, most progression in those who dropped out of therapy continued at higher rates (-0.9D), implying that treatment effects were real. It is plausible that those whose myopia progressed at a higher rate would be more likely to be referred to our clinic and participate in this study.

Although atropine 0.01% is becoming widely accepted due to minimal side effects and is the preferred treatment in several established practice guidelines, the reported efficacy is lower than that of high dose atropine.[27-29] The ATOM study showed twice as much control with atropine 0.5 vs. 0.01% (annual progression of SER: -0.24D vs -0.46D; of AL: 0.19mm vs 0.33mm) and the LAMP study found a similar dose effect when comparing 0.05 to 0.01% (annual progression of SER -0.27D vs. -0.59D; of AL 0.20mm vs. 0.41 mm).[15, 30] In our study on children with already high refractive errors (median SER: -5.03D), we aimed to achieve the best possible myopia control. Our data complement the earlier randomized controlled trials in Asians, as atropine 0.5% in our study demonstrated similar responses as ATOM II (Median annual SER:-0.25D; AL:0.11mm).[10, 15]

Seventeen children ceased therapy, most in the first months after the start, because of disturbances of accommodation or photosensitivity; 9 children stopped atropine because of an allergy, mostly due to an allergic conjunctivitis; and 2 stopped because of mild non-eye-related reasons. Nine children were lost to follow-up and did not return after their initial start of therapy. Serious systemic adverse events affecting heart, lung, or intestines described for other routes of atropine administration did not occur. Comparing our data to the 0.5% users of the ATOM study, we noticed many similarities.[15] The proportion of reported allergic conjunctivitis was slightly higher (7/124; 5.6%) probably related to the preservative benzalkonium chloride. Our study on mostly European children had more dropouts (N = 26; 21%) than studies on the more pigmented Asians (13.7%). Similar to ATOM, we found that photosensitivity complaints were predominantly reported in the first months of treatment; these diminished after 3 months.[15,19] Adverse events more often led to non adherence in teenagers than in younger children. Taken together, these observations suggest that remedies addressing the adverse events of high-dose atropine are warranted. We suggest the prescription of photochromic progressive spectacles and a cap for outdoor activity.

This clinical trial shows that findings from the ATOM II trial can be applied to clinical practice, also in Europe. The high dose atropine group in ATOM I & II experienced strong reduction of the annual myopia progression rate with close to stabilization of SER (+0.03D ±0.5) in the 1st year; and mild progression of -0.28D ± 0.92 in the 2nd year.[10] In our study, complete stabilization of SER (0.00D) was achieved during the 1st year. Progression of SER during the 2nd year was -0.41D, albeit somewhat higher than the reduction under trial circumstances. Two other observational studies reported long-term results after high dose atropine, both were executed in mild myopes > 25 years ago and showed close to stability of refractive error.[31, 32] Our study reports long-term follow up of more severe myopes on high dose atropine, and our data shows that progression during the 3rd year (-0.38D) did not increase further, showing stabilization of atropine efficacy. Despite the fact that myopia progression diminishes with age and some of the effect seen during our 3-year follow up reflects the natural reduction of progression, no significant difference (p = 0.08) in progression could be detected between children 10 years or younger, or older children. An intriguing question is whether atropine therapy has a lower effect on myopia progression in Europeans than in Asians. Comparison of annual progression rates shows that atropine 0.5% leads to -0.22D / year in Asian randomized trials and to -0.24D / year in other Asian studies, while atropine 0.5% in our European study leads to a median annual progression of -0.24D / year over a 3-year study period.[10, 21, 33] These figures suggest that ethnic differences in efficacy are minimal.

The biological effect of atropine, a non selective muscarinic receptor antagonist, remains unclear. The retina and sclera have been suggested as target sites since both tissues harbor muscarinic acetylcholine receptors (mAChR).[34] A study in guinea pigs found that atropine treatment decreased a regulator of G-protein signaling (a group of mAChRs) mRNA expression and increased collagen type I mRNA expression in sclera. More conclusive evidence whether blockage of mAChR directly interferes with axial elongation is lacking.[35] Several animal studies suggest that atropine therapy prevents eye growth through nitric oxide (NO) production; inhibition of NO interferes with atropine's effect.[36] Other indirect effects may be through dopamine, as studies have shown that intravitreal injections of atropine cause dopamine release in the retina.[37]

Both NO and dopamine are known to act as stop signals for myopia progression.[38]

We propose that atropine treatment should be customized according to age, risk of high myopia, and coping capacity with adverse events. One-third of the patients stayed on the starting dose 0.5% atropine, 29% responded so well after 1 year that the dose could be tapered. Lowering the dose did not lead to increased growth, and whether stopping causes a rebound phenomenon remains to be seen as this study continues. One-third responded rather poorly and was switched to the highest dose of atropine. Children who continued on atropine 0.5% or lower dosages showed a median annual progression rate of respectively -0.19D (IQR: 0.3) and -0.08D (IQR: 0.3). A stronger efficacy for atropine 1% has been well established by animal research as well as many clinical studies.[15, 25, 39] Children who needed the 1% treatment had an average median annual progression of -0.52D (IQR 0.4) while on atropine 0.5%, they had a younger median age ($p < 0.01$) and were more myopic at baseline, albeit not significantly (-5.81D IQR: 3.69 vs. -4.63D IQR: 3.47 $p = 0.22$). The ATOM study disclosed the same risk factors for poor responders.[40] Unfortunately, switching to atropine 1% in those responding poorly only slightly diminished growth further in our study. To prevent rebound growth, teenagers who reached stability of AL were tapered in atropine dose before stopping. This strategy prevented rebound of SER and AL, which did occur when high dose atropine was abruptly stopped in those with allergic reactions. These nine children had an initial good SER response of -0.4D/year (IQR: 0.7) in the 1st year increased to -0.9D/year (IQR: 1.3) in the 2nd year. (Table 2).

In summary, this real world study provided SER and AL outcomes for 0.5% starting dose atropine in European children with progressive myopia. We addressed side effects, prescribed photochromic progressive spectacles at the start of the study and diminished the risk of rebound growth by tapering the dose in children who had a stable SER and AL. With this regimen, 89/124 (71.8%) children stayed on therapy for 3 consecutive years. Median annual progression of SER for children on therapy was -0.25D (AL 0.11 mm), reflecting a nearly 75% reduction of myopia progression when compared with the rate before treatment. Our data imply that high-dose atropine should be considered a treatment option for severely progressing myopia, even in children with fair skin and blue eyes.

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Myopia management in the Netherlands

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Myopia management in the Netherlands

ABSTRACT

Purpose: A trend that myopia is becoming gradually more common is shown in studies worldwide. Highest frequencies have been found in East Asian urban populations (96.5%) but also a study in Europe shows that nearly half of the 25-29 year olds has myopia. With the increase in prevalence, high myopia, i.e. a spherical equivalent of -6 or more and an axial length of 26 mm or more is also on the rise. High myopia particularly carries a significant risk of ocular pathology related to the long axial length. This highlights the need for myopia management in children with progressive myopia, in particular progression to high myopia.

Recent findings: During the last decade, many intervention studies for myopia progression have emerged. Although lifestyle adjustments are effective, pharmacological and optical interventions have shown the highest efficacy on reduction of eye growth. High concentration atropine (0.5%-1.0%) shows the most reduction in axial length progression, but has drawbacks of light sensitivity and loss of accommodation. Nevertheless, when these side effects are mitigated by multifocal photochromatic glasses, the long-term adherence to high dose atropine is high. Lower concentrations of atropine are less effective, but have less side effects. Studies on optical interventions have reported reduction of progression for Ortho-K and multifocal contact lenses, but are in need for replication in larger studies with longer duration.

Summary: The field of myopia management is rapidly evolving, and a position on the best approach for daily clinics is desirable. Over the last 10 years, our team of clinical researchers has developed a strategy which involves decision-making based on age, axial length, position on the axial length growth chart, progression rate, risk of high myopia, risk profile based on lifestyle and familial risk, side effects, and individual preference. This personalised approach ensures the most optimal long-term myopia control, and helps fight against visual impairment and blindness in the next generations of elderly

RATIONALE

Myopia is becoming increasingly common in younger generations. With the increase in prevalence, more and more children also have high myopia, i.e. a spherical equivalent of -6 or more and an axial length of 26 mm or more. This is a clinically relevant problem, because especially high myopia is associated with an increased risk of ocular complications and irreversible visual impairment. Irrespective of the extent of myopia, the risk of myopic macular degeneration increases by 67% for each dioptre. This requires measures from eye care professionals. The progression of myopia during childhood can be inhibited by lifestyle changes and optical and pharmacological interventions. The rapid developments in myopia management and the high demand for measures make a position of experts on clinical management desirable. For this purpose, an expert group on myopia was established consisting of ophthalmologists, orthoptists, and optometrists. This group is internationally known for scientific research on myopia and has 10 years of experience in myopia management.

The problem

The main cause of myopia is an increase in eye axial length, especially in the posterior segment. The correlation between spherical equivalent and axial length in an eye with myopia is high (> 90%); a spherical equivalent of -6D or more is associated with an axial length of 26mm or more.[1, 2] The ocular morbidity increases per dioptre and per mm of axial length, and consists of myopic macular degeneration, retinal detachment, primary open angle glaucoma, macular hole, retinoschisis, and nuclear & posterior subcapsular cataract.[3-5] In a recent publication, Bullimore & Brennan showed that the risk of myopic macular degeneration increases by 60-70% per dioptre increase in myopic refractive error.[6] Every dioptre that is saved leads to a risk reduction of 30-40% in myopic maculopathy.[6] With the exception of cataract, myopic complications have a high risk of permanent visual decline. This is especially true for high myopia: one in three persons with high myopia (axial length 26 mm or more) develops visual impairment with age, 95% of those persons with axial length 30 mm or more.[2]
The number of people with myopia in the world has risen sharply in recent decades. The problem is greatest in strongly urbanised East and South East Asia; in countries such as Taiwan, South Korea and Singapore, 80-90% of 20-year-olds now have myopia.[7, 8] In Europe, 47.2% of 20-year-olds have myopia, while this was only 13.9% in the 1960s.[9] The prevalence of high myopia in Europe has risen from 1.0% to 5.3% and this rise is expected to continue. The number of visually impaired due to myopia will quadruple in 2050, and with that myopia will become the most important cause of blindness in Europe.[10]
These projections necessitate drastic actions. Because complications of myopia are largely irreversible in adulthood, the time to alter the visual prognosis of myopia lies in childhood.[8]

Eye growth

Adjustment of the congenital hyperopic refractive error occurs in childhood and is called emmetropization. It includes changes of the cornea, lens and axial length. The cornea undergoes the largest transition in the first 2 years of life; the lens has the largest change in thickness, curvature of the front and back surface, and refractive index during the first 10 years.[11] The axial length in emmetropes grows continuously up to ~ 15 years.[10] In myopia, normal growth is disturbed after emmetropization, and the eye grows beyond the focal point of the incoming light.[12] This growth in myopes can continue for up to 25 years. The average axial length of an emmetropic eye is 16.5 mm at birth and increases to 23.5 mm in adulthood.[13] Eyes with high myopia have an axial length of 26 mm or more; but 40mm eyes have also been described.[2] In particular children who develop myopia at primary school have a high risk of high myopia later in life.[14] The myopic refractive error that increases at adult age is usually the result of staphyloma development and does not represent active growth.[15]

Aetiology

Animal experiments have shown that myopia is not driven by excessive accommodation, but predominantly by hyperopic projection of light on the peripheral retina.[16] These are local visual mechanisms that do not depend on the macula or optic nerve.[17, 18]

The current consensus is that light projection on the retina triggers a signalling cascade, which flows into the sclera via the retina, retinal pigment epithelium (RPE), and choroid. There, re-modulation of collagen structures takes place that makes the eye longer.[19] The molecular structure of the signalling cascade is slowly becoming clearer, and dopamine is deemed to be an important player.[20] Animal experiments have shown that this neurotransmitter is secreted by the amacrine cells after light exposure, and acts as a stop signal for growth.[21-24] Other light-induced mechanisms have also been described, such as chromatic aberration.[25]

Genetic background

More than 400 genetic variants have been found in family studies and genetic studies in large consortia.[26] The identified genes are involved in neurotransmission, ion channels, connective tissue, the vitamin A cycle, and a plethora of other mechanisms, pointing towards a molecularly very complex signalling cascade.[19] The currently known genetic risk variants contribute ~ 12% to the variance of refractive error, but to 22% of that of high myopia.[27] The vast majority of the phenotypic variance is likely to come from gene-environment interaction.[28] Healthcare professionals should be aware of the increased risk of high myopia in children with a high myopic family predisposition. These children particularly need lifestyle advice, as the genetic predisposition makes children more susceptible to environmental drivers.[29] In addition, it is clear that myopic parents not only represent a genetic risk, they also create a more myopiagenic environment for their children.[30]

ENVIRONMENTAL FACTORS

Education & near work

Education is the oldest and most consistent risk factor for myopia.[28] People who have completed university or college are more often myopic than people with only elementary school.[31] In a large prospective cohort study among Dutch children, it has been shown that this is largely explained by a myopic lifestyle with little outdoor play and considerable hours of near-work during childhood. The association with education in the younger generations is diminishing as myopes are now deriving from all education levels.[32] There is growing evidence that performing many hours of near work, such as reading, increases the risk of myopia. The current evidence on near work is equivocal as consistency in the risk of this exposure in lacking, nevertheless, some studies find a significantly increased risk.[33] The greatest effect has been found for the performance of many continuous hours of near work and for a working distance < 30 cm.[33, 34] An important explanation for the latter is that peripheral hyperopia increases at a nearer gaze.[35, 36] Lower image quality due to a nearer gaze may also be a driver for ocular growth.

Outdoor exposure

Outdoor exposure during childhood is the most important lifestyle risk factor that is known thus far.[37] Outdoor exposure prevents or delays the onset of myopia and slows down progression.[38] From randomised trials in China and Taiwan in which school children were encouraged to go outdoors for up to 11 hours weekly, a risk reduction of 35% was observed for incident myopia and a 50% reduction in progression.[39] The protective effect of being outside is currently explained by a high light intensity leading to a higher retinal dopamine secretion, although other mechanisms may play a role as well.[40] The light intensity outdoors varies from 1000 lux on a cloudy day to more than 100,000 lux on a sunny day. The amount of lux inside is usually 500 or less. With artificial light one cannot equal the amount of lux outside. How many hours a child needs to be outside to be protected against myopia has been investigated in various studies. Most studies show a significant effect of outdoor exposure when children are exposed for at least two hours a day.[41-45]

MYOPIA MANAGEMENT

Several considerations need to be addressed when performing myopia control.

Axial length is the target

The occurrence of visual complications in myopia is strongly related to axial length, refractive error and age.[2] Reducing axial length growth and thereby reducing myopic refraction in adulthood is therefore the most important goal for the treatment of myopia.[46]

Axial length rather than myopic refractive error should be the primary target for myopia management. It therefore needs to be assessed at each visit.[47] Axial length does not have a stable growth rate with age, nor is it similar among the sexes and ethnicities, therefore, axial length should be related to its published growth curve per gender and ethnicity.[10] We generated axial length growth curves as a function of agebased on data from children with European ethnicity (Figure 1). Axial lengths which are on the 75th percentile or higher are at risk of high myopia. These lengths should be targeted with the most effective regimens, as only minimal progression will prevent high myopia. Axial lengths below the 75th percentile can cope with a more relaxed control.

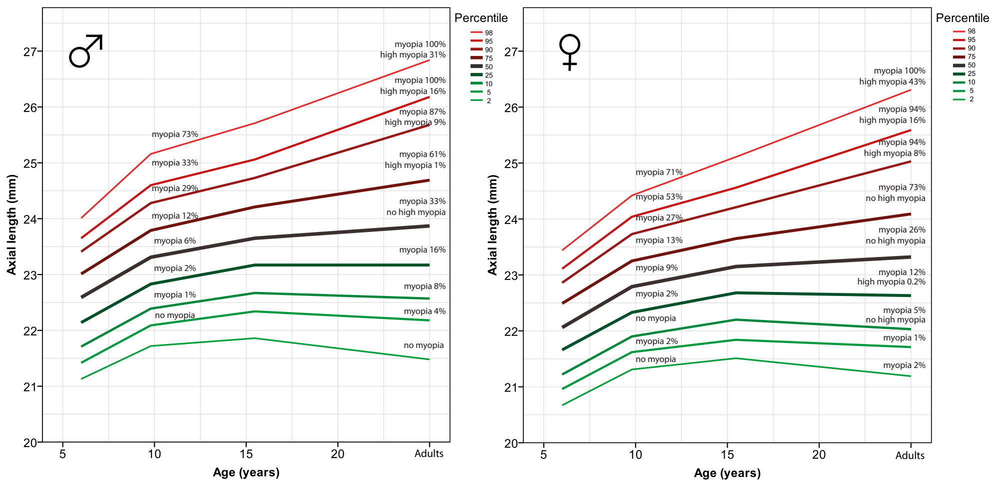

Figure 1: Growth curves with axial length (mm) versus age for European test subjects, boys (left) and girls (right), and with the risk of myopia in adulthood.

Lifestyle advice

Lifestyle advice should be given to all youth with progressive myopia, and encompasses outdoor exposure, close work, and working distance. Precise time limits with regard to smartphone or other screen use cannot be given at this time; the results of currently ongoing research will provide data on this in the future. In the Netherlands, we have joined efforts with professional Dutch organisations in youth health care, and designed a fact sheet. It recommends complete absence of close-up screen use for children up to 2 years old; maximum 1 hour/day^{-1} for children up to 5 years, and a maximum of 2 hours/day^{-1} for children aged 5-12 years.[48]
A practical advice that combines the recommendations is the 20-20-2 rule: after 20 min of close work, children should gaze in the distance for at least 20s; in addition, they should be outside for 2 hours/day^{-1}. In addition, close work should be performed at a distance of at least 30 cm.[30, 33, 34, 38]

Interventions

Complete stagnation of eye growth is currently not achieved with any therapy. After many trials, 3 interventions appear to inhibit progression clinically and statistically significantly: medication by atropine in different concentrations; and optically through orthokeratology (Ortho-K) and soft dual focus contact lenses. No or minimal protective effect has been shown for monofocal or bifocal glasses, and conventional monofocal rigid gas permeable contact lenses; under correction of myopia may even promote progression.[46, 49]

Atropine

It has been known for over 100 years that atropine eye drops stabilise myopia.[50] Atropine is a non-selective muscarinic receptor antagonist that is available as an eye drop in various concentrations (0.01% to 1%). The presence of muscarinic receptors has been demonstrated in the retina and in the sclera, but the precise role that they play in eye growth is not yet clear.[51, 52] However, it has recently been shown that atropine increases dopamine levels in the retina, and it was already established that dopamine inhibits eye growth. Another effect of atropine is an increase in NO, which can also serve as a mediator of eye growth.[53] For a long time, people were reluctant to use atropine as long-term treatment because of the pupil dilation, possibly causing phototoxicity, and accommodation paresis.[54] Phototoxic damage due to a high dose of atropine has been investigated by ERGs in the Atropine Treatment for Myopia (ATOM) study and it was found that the amplitudes and latency times in myopes with and without treatment were reduced by the same magnitude.[55, 56] Permanent damage to accommodation amplitude due to atropine use has also been investigated in ATOM, and investigators showed that 0.5% atropine after one year gives 0.44D less accommodation than 0.01% atropine. This reduction is not clinically significant.[57] Allergic conjunctivitis on the allergens in atropine unfortunately occurs in 3- 5% of users.[58, 59]

The effectiveness of atropine has been demonstrated in several studies. As early as 1971 an American ophthalmologist reported a study in which atropine was administered 1% daily in 150 children with myopia.[60] After one year, 75% showed no progression. From 1989 onwards, several randomised trials were conducted in Asia, of which ATOM from Singapore was the most important study.[61, 62] In this trial, 400 children were treated for two years with different concentrations of atropine or with a placebo, and this demonstrated a clear dose-response relationship. The decrease in spherical equivalent (SE) was significant for all concentrations, however, the decrease in axial length growth was only significant for atropine 0.5% and 1.0%, and axial length growth was even greater than placebo for the 0.01% dose. When treatment was discontinued after two years, a rebound effect of refractive error was observed for high dosages (0.5% and

1.0%), however, axial length was still most reduced for these concentrations. Another study, the Low-concentration Atropine for Myopia Progression (LAMP) Study, evaluated the two year effectiveness of three low dose atropine concentrations (0.01%, 0.025%, and 0.05%), comparing these to placebo during the first year. From baseline to 2 years, the 0.05% group showed an increase of 0.39mm ± 0.35, the 0.025% 0.50 ± 0.33, and the 0.01% group 0.58 mm ±0.33 . The placebo showed 0.43 ± 0.21 growth after the first year,[63] and 0.01% was not statistically significantly better than placebo. We conclude from this that 0.05% is the most effective of the low dosages, but still not as effective as the higher dosages 0.5% and 1%. Sudden discontinuation of 0.5% and 1% can indeed lead to an augmented rate of myopic refractive error increase, although this is not substantiated by axial length growth.[57, 58, 61, 64, 65] Nevertheless, we advocate a tapering schedule to low dose atropine when children have been treated with high dose atropine to minimise the risk of rebound. Evidence-based guidelines on how to perform tapering have not yet been established, and more research on this topic is needed.

To investigate coping and effect in European children, our research group initiated a real world effectiveness study for high dose atropine (0.5%) in Rotterdam in 2011. Seventy-seven myopic children with mean age 10.34 (± 3.21), axial length > 75th percentile, and myopia progression > 1D year^{-1} were treated with atropine 0.5%; after one year, progression was 0.04 mm year^{-1}. Seventy-eight per cent of the children adhered well to the treatment; however, children frequently reported photophobia (72%) and reading problems (38%).[59] The largest dropout occurred within the first month, after which it seemed easier for the children to tolerate the side effects. Nevertheless, we addressed these drawbacks and now prescribe multifocal, photochromic glasses at initiation of treatment with high dose atropine. When we prolonged the study, we found a myopic progression 0.16 mm year^{-1} for the second year and 0.14 mm year^{-1} for the third year. 74% managed to progress < 0.2 mm year^{-1} after 3 years. (Figure 2) This was significantly less than the 0.34 mm/yr for nontreated children with axial length > 75th percentile in the population-based children cohort Generation R, which served as a reference group. With optical correction, 73% of the children were able to adhere to treatment for the entire three year study period.

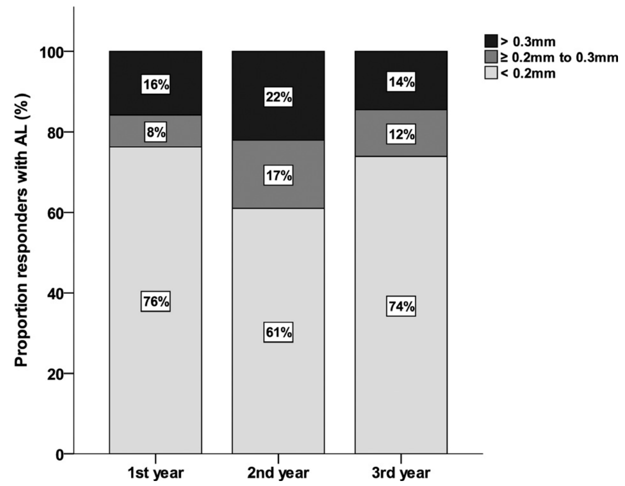

Figure 2: Proportion of good (light grey), moderate (dark grey), and poor (black) responders with respect to Axial Length in children with a starting dose of atropine 0.5% for progressive myopia.

Low dose atropine has lower risk of side effects.[66] At the lowest concentration 0.01%, only 4% complained about photophobia and 2% had reading complaints. The pupil dilation was < 1.5 mm and accommodation lag ~ 1D in both Asian and European populations.[58, 67] Optical adjustments were therefore not necessary. The LAMP study also addressed side effects of low dose atropine, and found a reduction of accommodation amplitude by -2.05D ± 3.19 and an increase of photopic pupil size by 1.25mm ± 1.13. The balance between efficacy and acceptable side effects makes this concentration attractive when less tight control is acceptable.

Orthokeratology

Orthokeratology or Ortho-K offers optical correction of myopia and astigmatism through the use of a specially shaped form-stable contact lens.[68, 69] By wearing this contact lens at night, myopia up to -4D can be corrected during the day without optical aids.[70] When wearing is discontinued, the original shape of the cornea will be restored after 2 weeks. Initially, Ortho-K lenses were only prescribed to replace optical correction during the day, but recently it has been demonstrated that they are also effective in myopia management.[71] The underlying mechanism is aimed at changing the peripheral hypermetropia in myopic children to a myopic defocus, thereby slowing down axial growth.[17]

Various studies on the efficacy of Ortho-K have been reported.[69, 71-77] In 2005, the Longitudinal Orthokeratology Research in Children (LORIC) study compared the axis length of 35 children (7-12 years) who wore Ortho-K lenses for a year with a historical cohort of children who had monofocal glasses and found a 54% decrease in the progression of axis length in the Ortho K group (0.29 vs. 0.54 mm). Other clinical studies reported a reduction between 32-55%. A recent meta-analysis of different Ortho-K studies with a total of 435 children showed an average inhibition of axial length growth of 0.26 mm year^{-1} relative to the control groups, a reduction of 43%.[78] Ortho-K has side effects as well. The most frequently reported complaints concern optical defocus; these can be solved by changing the lens fit so that the central part is placed in the visual axis. Milder corneal complications include a pigmented ring or a modified nerve pattern (fibrillary lines), or staining.[79-81] More severe complications are corneal infections, which are the reason why these lenses are discouraged by corneal specialists in some countries. Microbial keratitis (MK) is mostly the result of inadequate cleaning of the contact lens, and this occurs most commonly in early adolescence.[82-84] Data on the incidence of microbial keratitis can be found under the heading Risks of contact lens use in children.

Dual focus (bi or multifocal) contact lenses

Soft dual focus contact lenses were initially designed for presbyopia, but are now increasingly used for myopia management.[85] Only the lenses with center distance, i.e. central refraction correction for distance, have been investigated in myopia studies.[86] These lenses can have a gradual increase of plus addition (starting from 2.5D) in the periphery (progressive design) or in different zones (concentric design). The intention is to have optical correction in the fovea, and a myopic defocus in the periphery. This targets the hyperopic defocus in the periphery that leads to myopia progression.[36] Between 2011 and 2019, 9 randomised trials with soft dual focus contact lenses were published.[87-96] Four studies used lenses with a concentric design; the other studies used lenses with a progressive design. In two studies, the control group was corrected with monofocal glasses; in the others, the control group received monofocal soft contact lenses. The refractive error varied but averaged -2D (range -0.75 to -6.0) and 76% of children adhered to the treatment. The effectiveness of the dual focus lens with respect to myopia management was fairly consistent in the studies, and the reduction of both refractive error and axis length progression was between 29-59%. Although no complications were found, the dropout was greater in the contact lens group than in the spectacle group. The reasons for this were discomfort (11.7%), and problems with putting in and out (1.7%). The risk of keratitis is somewhat increased, as is for Ortho-K, see below.

Risks of contact lens use in children

The most clinically significant risk of contact lens use is a MK, which can result in corneal scars.[97, 98] The risk of MK is usually expressed as an incidence per 10,000 wearing years. With conventional GPR lenses, the lowest risk was found, namely 1.2 per 10,000 wearing years. Soft contact lenses, including dual focus lenses, have an incidence between 1.9 and 4.2 per 10,000 wear years.[99] Ortho-K lenses have an MK incidence of 13.9 per 10000 wear years and soft extended wear contact lenses have the highest annual incidence with 19.5 per 10,000 wear years.[100] The risk profile includes poor hygiene or rinsing with tap water, smoking, ordering via the internet, and little experience with contact lenses.[101, 102] In addition to MK, Ortho-K and soft extended wear also increase the incidence of infiltrates by other non-infectious pathogens. These can occur at an annual incidence 41.8 per 10,000 children, but rarely lead to permanent damage.[100]

In summary, given the complications, practitioners must be careful when advising contact lenses in children. It is important to provide comprehensive information on hygiene to patients and parents, and to emphasise that very strict compliance with lens cleaning is of great importance.

PRACTICAL GUIDELINE FOR MYOPIA CONTROL

How have we translated the evidence from scientific studies into our Dutch clinical practice? Taking age, expected growth rate of axial length without treatment, risk of high myopia, and efficacy of treatment into consideration, we developed the following strategy. When referred to us, a child with progressive myopia will be extensively examined at baseline. Patients and parents will be questioned about age of onset, family history, lifestyle with time spent on near work and outdoor exposure, accompanying health problems. Exams consist of cycloplegic refractive error, ocular biometry, slitlamp examination, and retinoscopy. If eye disorders underlying the myopic refractive error are suspected, corneal topography, retinal imaging, and/or electrophysiology will be performed. Axial length is plotted on the gender-specific growth curve, and risk of high myopia is evaluated. This usually helps tremendously in creating awareness of the problem in patients and parents. Every child with progressive myopia learns about the 20-20-2 rule, and information is provided on our website (www.myopie.nl). Efficacy, dropout rates, and serious adverse events are thoroughly discussed for each treatment.

We start children with axial length at the 75th percentile or above on atropine 0.5% eye drops. Multifocal photochromatic glasses with adequate distance correction and addition +3D are prescribed simultaneously. Follow up examinations with measurements of refractive error and axial length take place every six months, and then atropine concentrations can be increased or diminished depending on the progression of axial length. The axial length at follow up is plotted in the growth curves, allowing visualisation of the reduction in axial length percentile (Figure 3). This is an enormous stimulus for patients to adhere to treatment. Treatment will generally take place up to age 15 years; when axial length has stabilised (growth < 0.1 mm year^{-1}) for more than a year at this age, the atropine concentration can be gradually tapered.We stop treatment when significant growth is no longer expected, and the rate is ≤ 0.05mm year^{-1}. Some children in the highest percentiles may need to continue treatment after their 15th birthday.

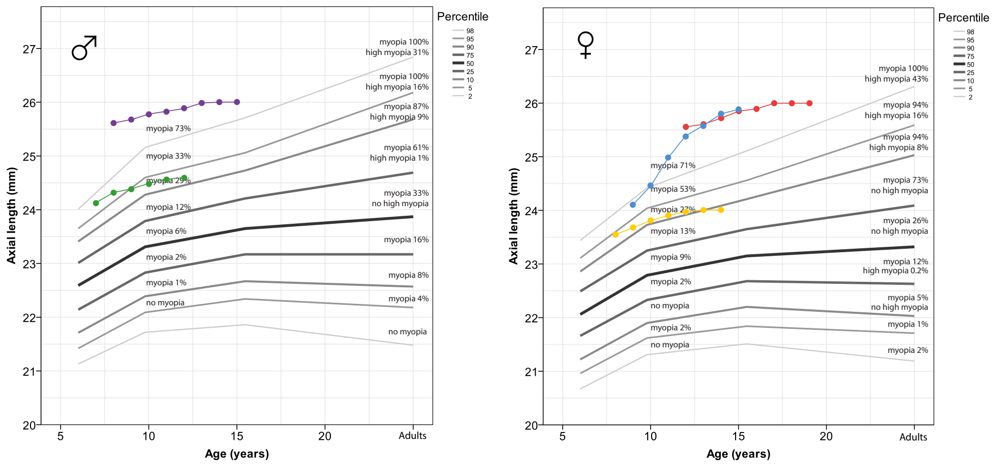

Figure 3. Visualisation of personal growth in five children over a six-to-seven year myopia management course (coloured lines).

Male patient purple started with 0.5% atropine at 8 years of age and continued for three years on this dose. We decreased the dose in year 3 from 0.25% to 0.1% to 0.01%. Because of the growth expectance he still uses atropine 0.01% at this point. His total increase in axial length was 0.41 mm over seven years of therapy, his spherical equivalent refraction (SER) progressed from -4.5 to -5.25. Male patient green started with 0.5% atropine at 7 years of age and continued for two years on this dose. We decreased the dose in years 3 and 4 to 0.25%. His total increase in axial length was 0.74 mm over six years of therapy, his SER progressed from -3.25 to -4.25. Female patient blue started with 0.5% atropine at 9 years and increased the dose to atropine 1% after two years. She stayed on 1% atropine in years 3 and 4 and tapered to 0.5%, 0.25% and 0.1% in years 5, 6 and 7. Her total increase in axial length was 1.99 mm over seven years of therapy, her SER progressed from -2.75 to -8.0. She has poor response and a combination therapy of dual focus lenses can be considered. Female patient red started with 0.5% atropine at 12 years of age and continued for three years on this dose. We decreased the dose in years 3, 4 and 5 to 0.25% to 0.1% to 0.01%. She kept using 0.01% during her sixth year of treatment but stopped thereafter. The last year remains stable without therapy. Her total increase in axial length was 0.45 mm over seven years of therapy, her SER progressed from -6.25 to -7.00. We will remain to follow up till the age of 21. Female patient yellow started with 0.5% atropine at 8 years of age and increased the dose to atropine 1% after one year. She stayed on 1% atropine in years 2 and 3 and tapered to 0.5%, 0.25% and 0.1% in years 4, 5 and 6. Her total increase in axial length was 0.47 mm over six years of therapy, her SER progressed from -2.75 to -4.0.

Children with axial length below the 75th percentile can be controlled with less effective regimens, with the advantage of having less side effects. We discuss all treatment options with the patient and parents and make a shared decision on low dose atropine (0.05%), Ortho-K, or multifocal contact lenses. Follow up examinations are also every six months, and axial length is plotted in the growth curve at every visit. A contra indication for high dose atropine is age below 6 years, for contact lenses age below 8 years.

Ocular morbidity increases per millimeter of axial length. With the current knowledge about the long-term consequences of myopia, professionals providing eye care for children cannot and should not focus solely on diseases that present during childhood. Prevention of blinding disorders that occur later in life is just as important. We advocate the execution of myopia control by professionals with adequate knowledge of myopia causes, course, and consequences, who target and measure axial length at each visit, and who have a good inter-professional network if other strategies are needed. For instance, children < 6 years who present with axial length ≥ 75th percentile should be referred to a pediatric ophthalmologist for diagnostics. To optimise the outcome for all myopic children at risk of visual impairment, collaboration and exchange of knowledge between all disciplines in eye care is warranted.

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6.

General discussion and future prospects

Parts of this chapter were obtained from the published paper:

Klaver CCW, Polling JR, Enthoven CA. 2020 as the Year of Quarantine Myopia. JAMA Ophthalmol 2021;139(3):300-1.

General discussion and future prospects

In this thesis, we investigated the prevalence of myopia in populations, evaluated risk factors, studied progression of spherical equivalent and axial length, and performed intervention studies for myopia progression to prevent the development of high myopia. We developed strategies for myopia management for the professional practice. The main findings of this thesis will be discussed and the clinical implications and future prospects considered.

Methodological Considerations

In this thesis a number of cohorts were used to answer the different questions. Specific methodological issues have been addressed in the papers. Here we discuss some common methods and problems we encountered.

The different cohorts presented in this thesis provide an overview of the current knowledge on the development and treatment of refractive errors in childhood. The overall question is: How well can myopia during childhood and puberty be managed through lifestyle and intervention and can this permanently change the final degree of myopia in adulthood? In the introduction we described the cohorts of children and young people who participated in the various sub-studies. We used these different cohorts because not all sub-questions could be solved with the same cohort. For example, in Chapter 2 we used an un-vision-screened cohort versus a vision-screened cohort. Although the prevalence of refractive errors in the populations is similar, the majority of children from the unscreened population lack adequate correction. As we know, this has implications for myopia, as under correction shows faster progression. Chapter 3, Myopia development in European populations, includes two complementary publications that are often used in myopia control statements and protocols in the Netherlands and Europe. The first part discusses the normative ocular growth curves for children ages 6 to young adults, illustrating the risk of development and progression of myopia. This article shows tools relevant to decisions about initiating treatments to slow the progression of myopia. These guidelines are important for parents/carers, clinicians and health insurers. Whether we can really compare the two publications remains a question we won't know until both axial length and spherical equivalent studies show us the development of myopia from onset to adulthood. Chapter 4, Myopia management with atropine, presents two publications reporting observational studies on the use of medium and high concentration atropine to slow the progression of myopia. The question of whether high-dose atropine can be used for myopia control in the daily clinic is addressed here. Selection bias for both studies appears to be present because the patient population comes from our specialized referral centre for high myopia. A follow-up study of the treatment of a variety of progression of myopia with a high dose versus a low dose will provide a better answer as to which type of treatment is indicated for which degree of progression. Chapter 5, Myopia management in the Netherlands presents our developed myopia control protocol. It provides a "how-to" guide, but as not all recommendations can be linked to effectiveness and evidence, this paper is a work in progress and will change in the coming years as more dosing studies in atropine, dual-focus contact lenses and peripherals defocusing glasses are published.

In general, more real life studies should be available to confirm the outcomes of the current randomized clinical trials. There is an abundant request for myopia control and as some form of myopia management becomes the norm, a proper (inter)national registration of real world therapies with axial length and spherical equivalent as outcome will potentially answer this question.

Importance of lifestyle

Because myopia is also increasingly common in Europe the rational for myopia management is evident.[1] Of the twenty year olds, 1 in 2 is now near-sighted and the prevalence is expected to increase even further.[2] High myopia in particular increases the risk of complications considerably, but less myopic persons are also at risk.[3] For example, there is already a 2-8x increased risk of glaucoma, retinal detachment, and myopic macular degeneration for refractive errors up to -6D, and this risk rises to nearly 500x for refractive errors greater than -6D. Of the high myopes, 1:3 is visually impaired in both eyes.[4] This visual impairment generally occurs after the 50th year on.[3]

When children are first diagnosed with myopia, I strongly recommend lifestyle advice.[5, 6] To make the advice easy to implement in daily life, we have developed the 20-20-2 rule which is now echoed all over the Netherlands and in many other places in the world:

After 20 minutes of close work, children should gaze at objects in the distance for at least 20 seconds, and they should be outsidefor a total of at least 2 hours per day.[5]

Controlled and randomized trials show a significant effect of being outdoor when children are exposed to a minimum of 2 hours of outdoor light per day.[7, 8] Studies also show that continuous near work and working distances of less than 30 centimetres increase the risk of myopia development.[9] Therefore, playing outside and avoiding long hours of near work is an intervention in itself.

With the current global quarantine measures in place, this gave us the possibility to view the effects of myopic risk factors in a population that already is exposed to a lot of myogenic risk factors. As an important reminder how unfavourable lifestyle can boost myopia incidence in children, the paper by Wang et al., shows us that the lockdown due to the COVID-19 pandemic has had dramatic impact on myopia prevalence among the youngest children.[10] We were given the opportunity to write an editorial on this paper that presented the data of myopia progression during a rigorous quarantine. 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.

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 non cycloplegic photo refraction in schoolchildren aged 6 to 13 years; during the 3 months that followed, they analyzed all data and prepared for publication.

To assess temporal trends across age groups, the authors[10] 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. 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.

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.[11] 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 behaviour, 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.[12-14] 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 myopia genesis. Adhering to the 20-20-2 rule even in a pandemic, might control a wave of quarantine myopia.

Myopia management

More intense interventions, such as pharmacological and optical interventions, have received recognition for their ability to control myopia after randomized controlled trials: (a) atropine atvarious concentrations; (b) orthokeratology; (c) soft bifocal or multifocal contact lenses.[15] Special spectacle lenses (Defocus Incorporated Multiple Segments) and light therapy with certain wavelengths show promising results in the first publications, but are currently investigated in RCT's or in need for replication in different target groups.[16]

In my view, start of intervention should be considered as soon as possible after first diagnosis. A first step is then to evaluate the final refractive error as an adult by plotting the child's axial length on the axial length growth curve developed by our research group.[5] The percentile on which the axial length is plotted on the curve predicts the risk and level of high myopia, and in particular predicts the progression during the years to come. With this prediction model, the history of progression, and the family history, an assessment can be made forthe strength of inhibition which is desired.

Special attention should be given to children whose refraction is higher than the age (up to the age of 8 years), the percentile of axial length ≥ P98, low unexplained visual acuity, complaints of night blindness or photophobia, ora positive family history for genetic disorders. Those children should be evaluated with care and have proper diagnostics (e.g. imaging and electrophysical testing) before initiating myopia management.

From the 75th percentile on the growth curve, the risk of high myopia development at a later age increases substantial. In these cases, I recommend close monitoring and a very effective intervention, a starting dose of 0.5% atropine.[17] For axial lengths below the 75th percentile on the curve other therapies can be recommended, in close consideration of the wishes of caregivers and patients.

Determination of the success of therapy can be difficult. The remaining axial length growth after therapy must be evaluated based on age and the initial percentile of axial length growth.[18] Close monitoring of annual progression of axial length should be the daily practice of clinicians in myopia management. Determination of cessation of therapy is also challenging. I recommend taking this into consideration only when progression has dropped under 0.1 mm/year and the child has reached the age of 15 years.

When stopping atropine, especially the refraction can get a rebound. The axial length rebounds which have been reported after cessation of atropine are negligible.[19] When therapy has been stopped, the axial length increase tends to be remarkably close the original percentile in the growth curve. Although not grounded by evidence, our group recommends tapering of the atropine dose before stopping.

Groups at risk of progressiondespite therapy

Most intervention studies (atropine, ortho-K, and multifocal contact lenses) found a percentage of about 15% for non-response in their intervention group.[20] Many of these children already have extremely long eyes at the start of the study with very high rates of progression. When atropine has been prescribed is used, lower dosages can be increased up to 1%. Studies allowing variable concentrations show that the number of non-responders decreases with increasing dose. Nevertheless, a small proportion of cases continuous to show non-response.[5] Risk factors for a low response to therapy have been identified in many studies, and include younger age (less than 9 years), rapid progression in the past year, high myopia at start of treatment, myopic parents, and strong lifestyle risk factors.[17]

In our atropine studies described in this thesis, we observed a considerable age effect, i.e., more progression at very young age despite therapy. We also noticed this in our large population cohort studies. The mean increase in axial length and spherical equivalent in children under 10 is twice as high as in children 10-13 years old.[18] Very fast growth at young ages seems to be less controllable, and is in need for more effective treatments than currently available.

Improving management

Due to the rapid increase in possibilities for myopia control, recent insights from the scientific literature are essential to get a clear picture of what a clinician should offer to the myopic child.[21] The field of myopia is very divided with respect to the treatment method for myopia control, and the choice of treatment often does not reflect the need of the patients. Many eye care providers oppose to the use of high-dose atropine, although they usually accept that high concentrations have the highest efficacy. It is important to make an individualized risk score for each patient with myopia progression to select the most appropriate therapy for that person. This requires consideration of the following items:

- age
- position on the axial length growth curve
- risk of high myopia
- risk profile based on lifestyle and motivation to change this
- familial risk
- expected side effects
- individual preference

This personalized approach, applied together with the principles of shared decision making, willen sure the most optimal control of myopia in the long term. These items have proven to be moderators of myopia progression in epidemiological studies but real world algorithms will need further evaluation. When choosing for high dose atropine, strict supervision with proper fitting of multifocal photochromic glasses is essential. High dose should be avoided during the sensitive period (0-4 years) because ofthe risk of creating an amblyogenic factor.[22] Our clinical atropine studies have shown that high dose atropineis an effective treatment option for severely progressive myopia, also in children of European ethnicity.

Future prospects

Ophthalmic complications due to myopia will soon be the greatest cause of visual impairment in the Netherlands. This requires a major approach to this problem in all areas. Just like combating increased BMI and obesity in children, myopia should also be on the national agenda as a health risk. We need to counteract the rising prevalence and expose children to more outside light. Who is responsible for this?

First, of course, the educators of schools play a key role. Parents cannot be held solely responsible for the total of 2 hours/day outdoor exposure. They need help, and thus schools should pitch in. Schools should increase outdoor extracurricular activities to help slow eye growth and reduce or at least delay incident myopia. Second, clinicians and eye care providers need to do more: youth health doctors, opticians, optometrists, orthoptists, and ophthalmologists should focus more on prevention and lifestyle counselling in children at risk, and collaborate better when treatment of progressive myopia is needed. Third, prevention of myopia should not only be sought by increasing outdoor exposure. Suppliers of smartphones and tablets must also take their social responsibility and integrate software for children to help the mad here to the 20-20-2 rule. Fourth, government agencies should support initiatives for awareness programs that address the problem in all social classes of the population. In addition, they should add screening measures within the existing screening programs to measure eye growth early in life and offer personalized lifestyle advice and possibilities to treat (pre-)myopia. Some intervention studies are now treating pre-myopia by decreasing peripheral hyperopic refraction through bifocal or multifocal contact lenses or glasses.

As with any intervention, consideration must be given to deal with non-compliance. In the case of amblyopia treatment, we know that non-compliance is one of the most principal factors for treatment failure. Noncompliance has not been addressed very well in myopia control studies, and better insight into this problem will help find solutions.

To date no intervention can completely stop myopia progression. Although there are three highly potent therapies, a combination of these therapies has not been compared well in prospective randomized studies. Combination therapy offers an opportunity to treat myopia progression which is not controlled well with monotherapy. Novel therapies could also thread a needle, as special spectacle lenses (among which the Defocus Incorporated Multiple Segments and Diffusion Optics Technology lenses) and light therapy with certain wavelengths show promising effects.

Concluding remark

My thesis built on the epidemiologic groundwork laid by our research group and steered the myopia research towards intervention studies. I have shown that atropine in high dose is well accepted and effective in myopic children under real world conditions. I have helped develop a strategy to implement this treatment with good adherence and established the guidelines for myopia control clinics in the Netherlands. Refinement of who to treat with what and when will be the focus of my future research.

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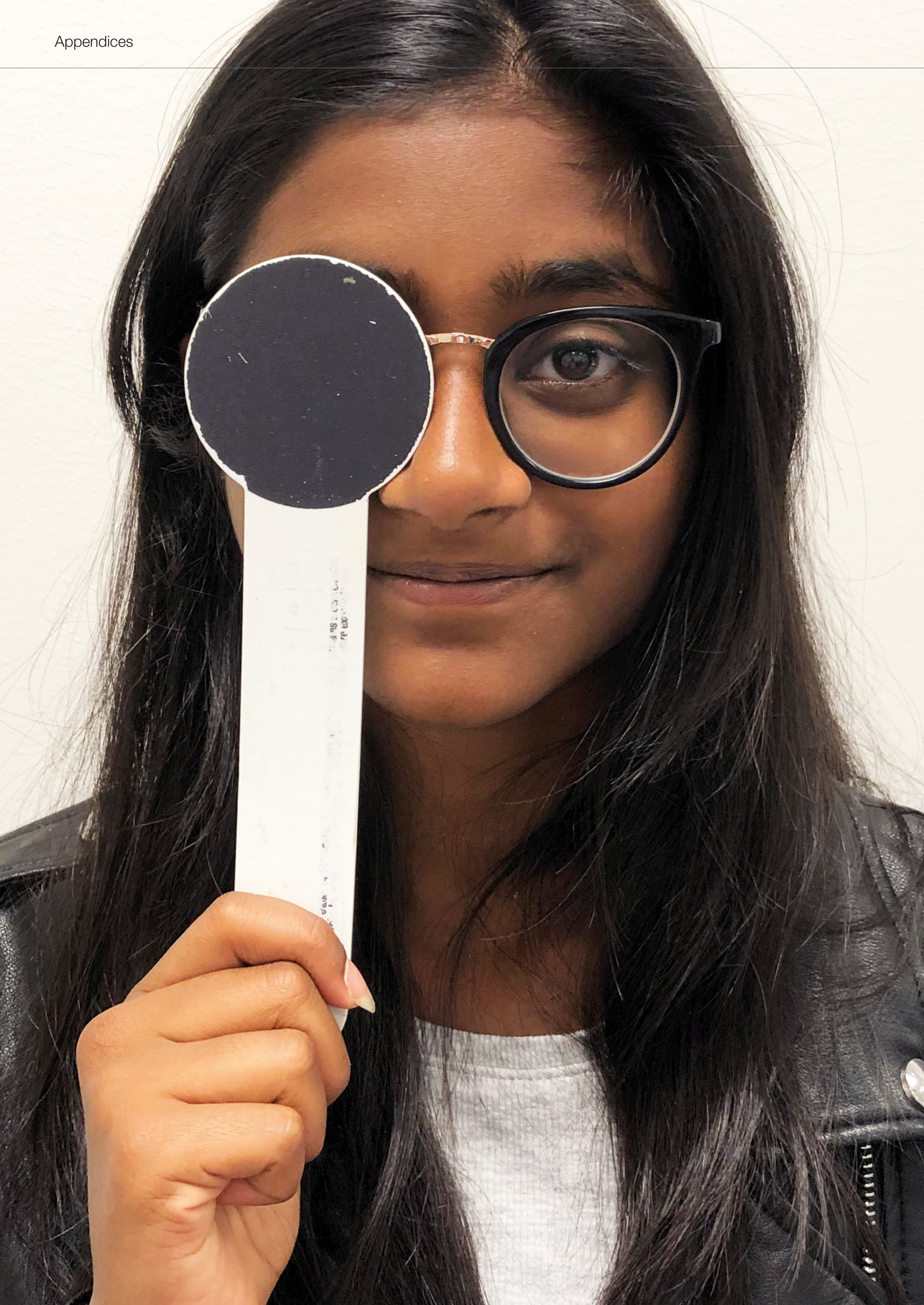
7.

Appendices



I

English summary

Myopia is becoming a major epidemic not only in Asia but also in many other parts of the world. The increasing incidence of myopia is directly related to changes in the lifestyle of children, they play too little outside and spend too much time indoors looking at their screens. There is concern about the increasing prevalence of myopia because people with myopia are more likely to develop sight-threatening complications later in life, such as cataracts, glaucoma and myopic macular degeneration. Therefore, there is an urgent need for interventions that inhibit myopia progression. Although there is a lot of evidence about which therapies are effective, little has been implemented in the daily practice of eye care providers.

The main objectives described in this thesis were: (1) what are the eye problems occurring in early childhood, (2) how does the eye grow and how does this effect myopic refractive error in adulthood, (3) can high dose atropine be applied for myopia control in the everyday clinic and (4) what can be recommended to general eye care practitioners with respect to management of myopia progression.

Chapter 1 provides a general introduction to the development of refractive error from a historic perspective and myopia in particular. Basic concepts about therapies are discussed. **Chapter 2** discusses the findings in ophthalmic paediatric populations. In **Chapter 2.1** we investigated the current ophthalmological findings in a previously vision screened urban population; the Generation R study. Nearly 10% of all children that visited the research center at the age of six years had contacted an eye-care provider. Another 5% had an insufficient visual acuity. Myopia was found in 2.6% of the children. Remaining amblyopia was found in less than 0.5% of all children and only 3 out of the 115 casus with strabismus were reported as an incidental finding. Pediatric vision screening strongly reduced uncorrected refractive errors and the prevalence of insufficient treated amblyopia. In **Chapter 2.2**, we studied visual acuity and refractive errors in a rural European pediatric population that had not received vision screening. Myopia prevalence was slightly lower (2.2%) at the age of 6 years. Amblyopia prevalence, however, was much higher: 3.1%. A national screening program will help reduce amblyopia prevalence and leads to reduction of uncorrected refractive errors.

In **Chapter 3**, we explored the natural course of two important parameters for myopia: axial length (AL) and spherical equivalent of refraction (SER). We generated percentile curves for European children, which can be used to estimate the risk of high myopia in adulthood. In **Chapter 3.1** this was done in the using different population studies; Generation R study (6 and 9 year olds), Avon Longitudinal Study of Parents and Children (15 year olds), and the adults from the Rotterdam Study III. Mean AL was 22.36 mm at 6 years, 23.10 mm at 9 years, 23.41 mm at 15 years, and 23.67 at adulthood. AL differences after the age of 15 years occurred only in the upper 50%. These figures provide normative values for AL that can be used to monitor eye growth in European children. **Chapter 3.2** investigated myopia progression by means of SER from the first pair of glasses to the final degree of myopia at adult age. Data from the Drentse Refractive Error and Myopia Study was obtained from a branch of opticians in the north of the Netherlands. Those with first prescription before the age of 10 years showed the strongest progression and had a more negative final SER (-4.48 diopters). All children who developed SER more than -3 diopters at 10 years were highly myopic (more than -6 diopters) as adults. Myopia progression diminished with age; all refractive categories stabilized after age 15 years except for SER more than -5 diopters who progressed up to -0.25D annually until age 21 years. SER at 10 years is an important prognostic indicator and will help determine treatment intensity. These figures provide normative values for myopic SER that can be used to monitor progression in European children.

Chapter 4 focusses on the treatment of progressive myopia by means of high-dose atropine. This part explores the effectiveness of atropine 0.5% at 1 year and 3 years follow-up as a treatment for progressive high myopia and adherence to therapy in children from the Netherlands. In **Chapter 4.1** we examined SER and AL at 1, 2 and 12 months after initiating therapy. Nearly 80% of children adhered to atropine treatment for 12 months, those who stopped did this primarily within the first month. Reported adverse events were photophobia (72%), followed by reading problems (38%), and headaches (22%). The progression rate of SER before treatment diminished substantially during treatment. Despite the relatively high occurrence of adverse events, atropine can be an effective and sustainable treatment for progressive high myopia in Europeans. **Chapter 4.2** describes the 3 year follow-up data of this prospective study. After the first year adjustments to the dose were made in case of low (AL more than 0.3 mm/year) or high response (AL less than 0.1 mm/year) of AL. More than 70% of the children were persistent to therapy throughout the three year follow-up. Annual progression of SER for these children was -0.25 diopter and of AL 0.11mm. Insufficient response was found in 36% and were assigned to atropine 1% and good response was seen in 29% and underwent tapering in dose. A total of 19% stopped due to adverse events, including allergy and photophobia. In this three year study, a starting dose of atropine 0.5% was associated with decreased progression in European children in children at risk of developing high myopia in adulthood.

The field of myopia management is rapidly evolving, and a position on the best approach for daily clinics is desirable. In **Chapter 5**, we developed a protocol for myopia management that was based on the input of an expert group on myopia consisting of ophthalmologists, orthoptists, and optometrists. Over the last 10 years, this team of clinical researchers has developed a strategy which involves decision-making based on age, axial length, position on the axial length growth chart, progression rate, risk of high myopia, risk profile based on lifestyle and familial risk, side effects, and individual preference. This personalised approach ensures the most optimal long-term myopia control and helps the fight against visual impairment and blindness in the next generations of elderly.

Lastly, **Chapter 6** provides an insight in how the last pandemic underlines the importance of lifestyle measures for young children and gives a general interpretation and implication of the main findings in this thesis. This chapter also addresses considerations, clinical implications, and future prospects.

II

Nederlandse samenvatting

Myopie lijkt een grote epidemie te worden, niet alleen in Azië maar ook in veel andere delen van de wereld. De toenemende incidentie van myopie houdt direct verband met veranderingen in de levensstijl van kinderen, ze spelen te weinig buiten en kijken te veel naar hun beeldschermen. Er is bezorgdheid over de toenemende prevalentie van myopie, omdat mensen met myopie later in hun leven meer kans hebben op gezichtsscherpte bedreigende complicaties, zoals netvlies loslating, glaucoom en myope maculadegeneratie. Daarom is er een dringende behoefte aan interventies die de progressie van myopie remmen. Hoewel er veel wetenschappelijk bewijs is over welke therapieën effectief zijn, is er weinig geïmplementeerd in de dagelijkse praktijk van oogzorgaanbieders.

De belangrijkste doelstellingen beschreven in dit proefschrift waren: (1) wat zijn de oogproblemen die optreden tijdens de vroege kinderjaren, (2) hoe groeit het oog en hoe beïnvloedt dit de myope refractieafwijking op volwassen leeftijd, (3) kan een hoge dosis atropine worden toegepast voor myopie controle in de dagelijkse kliniek en (4) wat kan worden aanbevolen aan oogzorgaanbieders met betrekking tot myopie controle.

Hoofdstuk 1 geeft een algemene inleiding in de ontwikkeling van refractie afwijkingen vanuit historisch perspectief en myopie in het bijzonder. Basisbegrippen over therapieën worden besproken. **Hoofdstuk 2** bespreekt de oogheelkundige bevindingen in pediatrische populaties. In **Hoofdstuk 2.1** onderzochten we de huidige oogheelkundige bevindingen in een gescreende populatie van kinderen geboren in Rotterdam; het Generation R-onderzoek. Bijna 10% van alle kinderen die op zesjarige leeftijd het onderzoekscentrum bezochten, was eerder bekend bij een oogzorg aanbieder. Nog eens 5% had een onvoldoende gezichtsscherpte. Myopie werd gevonden bij 2.6% van de kinderen. Resterende amblyopie werd gevonden bij minder dan 0.5% van alle kinderen en slechts 3 van de 115 gevallen met scheelzien werden als nieuwe bevinding gemeld. Vroegtijdige visusscreening verminderde sterk de ongecorrigeerde refractieafwijkingen en de prevalentie van onvoldoende behandelde amblyopie. In **Hoofdstuk 2.2** bestudeerden we gezichtsscherpte en refractieafwijkingen in een niet-stedelijke Europese populatie die niet gescreend was. De prevalentie van myopie was iets lager (2.2%) op de leeftijd van 6 jaar. De prevalentie van amblyopie was echter veel hoger: 3.1%. Een landelijk screeningsprogramma voor visusstoornissen zal de prevalentie van amblyopie helpen verminderen en leidt tot vermindering van ongecorrigeerde refractieafwijkingen.

In **Hoofdstuk 3** hebben we het natuurlijke verloop van twee belangrijke parameters voor myopie onderzocht: axiale lengte (AL) en sferisch equivalent van refractie (SER). We hebben percentielcurven gemaakt voor Europese kinderen, die kunnen worden gebruikt om het risico op hoge myopie op volwassen leeftijd in te schatten. In **Hoofdstuk 3.1** is dit gedaan in het gebruik van verschillende populatiestudies; Generation R-studie (6 en 9-jarigen), Avon Longitudinal Study of Parents and Children (15-jarigen), en de volwassenen uit de Rotterdam Study III. De gemiddelde AL was 22.36 mm bij 6 jaar, 23.10 mm bij 9 jaar, 23.41 mm bij 15 jaar en 23.67 bij volwassenen. AL-veranderingen na de leeftijd van 15 jaar kwamen alleen voor bij de bovenste 50%. Deze cijfers bieden normatieve waarden voor AL die kunnen worden gebruikt om de ooggroei bij Europese kinderen te vervolgen. **Hoofdstuk 3.2** onderzocht de progressie van myopie door middel van SER vanaf de eerste bril tot de myopie op volwassen leeftijd. Gegevens uit de Drentse Refractive Error and Myopia Study zijn verkregen van een keten van opticiens in het noorden van Nederland. Degenen met een eerste myope bril vóór de leeftijd van 10 jaar vertoonden de sterkste progressie en hadden een meer negatieve SER (-4.48 dioptrieën) op volwassen leeftijd. Alle kinderen die een SER van meer dan -3 dioptrieën ontwikkelden voor het 10^{e} jaar waren allemaal zeer bijziend (meer dan -6 dioptrieën) als volwassenen. De progressie van myopie nam af met de leeftijd; alle refractie categorieën stabiliseerden na de leeftijd van 15 jaar, behalve voor SER meer dan -5 dioptrieën die jaarlijks tot -0.25D toenamen tot de leeftijd van 21 jaar. SER op 10 jaar is een belangrijke prognostische indicator voor risico op hoge myopie en zal helpen bij het bepalen van de behandelingsintensiteit. Deze getallen bieden normatieve waarden voor SER ontwikkeling die kunnen worden gebruikt om de progressie bij Europese kinderen te volgen.

Hoofdstuk 4 richt zich op de behandeling van progressieve myopie door middel van een hoge dosis atropine. Hierin onderzoeken we de effectiviteit van atropine 0.5% na 1 jaar en 3 jaar follow-up als behandeling voor progressieve hoge myopie en therapietrouw bij kinderen uit Nederland. In **Hoofdstuk 4.1** onderzochten we SER en AL op 1, 2 en 12 maanden na het starten van de therapie. Bijna 80% van de kinderen hield zich gedurende 12 maanden aan de atropinebehandeling, degenen die stopten deden dit voornamelijk binnen de eerste maand. Gemelde bijwerkingen waren fotofobie (72%), gevolgd door leesproblemen (38%) en hoofdpijn (22%). De progressiesnelheid van SER vóór de behandeling nam aanzienlijk af tijdens de behandeling. Ondanks het relatief vaak voorkomen van bijwerkingen, kan atropine een effectieve en duurzame behandeling zijn voor progressieve hoge myopie bij Europese kinderen. **Hoofdstuk 4.2** beschrijft de 3 jaar follow-up gegevens van dit prospectieve onderzoek. Na het eerste jaar werd de dosis aangepast in geval van een lage (AL meer dan 0.3 mm/jaar) of hoge respons (AL minder dan 0.1 mm/jaar) van AL. Meer dan 70% van de kinderen bleef therapietrouw gedurende de drie jaar durende follow-up. De jaarlijkse progressie van SER voor deze kinderen was -0.25 dioptrie en van AL 0.11 mm. Onvoldoende respons werd gevonden bij 36% en werd toegewezen aan atropine 1% en een goede respons werd gezien bij 29%, bij deze kinderen werd de dosis afgebouwd. In totaal 19% van de kinderen stopte vanwege bijwerkingen, waaronder allergie en fotofobie. In deze drie jaar durende studie werd een startdosis van 0.5% atropine geassocieerd met verminderde progressie bij Europese kinderen met een risico op het ontwikkelen van hoge myopie op volwassen leeftijd.

Het gebied van myopiemanagement is een snel veranderend veld en een standpunt over de beste aanpak voor dagelijkse klinieken is wenselijk. In **Hoofdstuk 5** hebben we een protocol voor myopiemanagement beschikbaar gesteld dat gebaseerd was op de input van een expertgroep op het gebied van myopie bestaande uit oogartsen, orthoptisten en optometristen. In de afgelopen 10 jaar heeft dit team van klinische onderzoekers een strategie ontwikkeld die besluitvorming omvat op basis van leeftijd, axiale lengte, positie op de aslengte groeicurves, progressiesnelheid, risico op hoge myopie, risicoprofiel op basis van levensstijl en familiair risico, bijwerkingen en individuele voorkeur. Deze gepersonaliseerde aanpak zorgt voor de meest optimale beheersing van myopie op de lange termijn en helpt bij de bestrijding van slechtziendheid en blindheid bij de volgende generaties ouderen.

Hoofdstuk 6 tenslotte geeft inzicht in hoe de laatste pandemie het belang van leefstijlmaatregelen voor jonge kinderen onderstreept en geeft een algemene interpretatie en implicatie van de belangrijkste bevindingen in dit proefschrift. Dit hoofdstuk gaat ook in op overwegingen, klinische implicaties en toekomstperspectieven.