Refractive and axial development of the growing eye

Kumulative Dissertation

Zur Erlangung des akademischen Grades
Dr. rer. med.

An der Medizinischen Fakultät

der

Universität Leipzig

vorgelegt von:	Carolin Truckenbrod
Geburtsdatum/ Geburtsort:	15.06.1989/ Leipzig
Angefertigt an/ in:	medizinische Fakultät der Universität Leipzig
Betreuer:	Prof. Dr. med. Wieland Kiess/ Christof Meigen
Beschluss über die Verleihung des Doktorgrades vom:	24.05.2022

Vorbemerkung

Für diese Dissertationsschrift wurde die Form der Publikationspromotion gewählt. In den eingefügten Originalpublikationen werden alle verwendeten Materialien und Methoden sowie die Ergebnisse ausführlich beschrieben und diskutiert.

Bibliografischer Nachweis der Publikationen:

Truckenbrod C, Meigen C, Brandt M, et al. Reference curves for refraction in a German cohort of healthy children and adolescents. *PLoS ONE*. 2020;15(3):e0230291. doi:10.1371/journal.pone.0230291.

Brandt M, Truckenbrod C, Meigen C, et al. Impaired visual acuity caused by uncorrected refractive errors and amblyopia in a German paediatric cohort. *Ophthalmic Physiol Opt*. 2021;41(1):42-52. doi:10.1111/opo.12748.

Truckenbrod C, Meigen C, Brandt M, et al. Longitudinal analysis of axial length growth in a German cohort of healthy children and adolescents. *Ophthalmic Physiol Opt*. 2021. doi:10.1111/opo.12817

Brandt M, Meigen C, Truckenbrod C, et al. Refractive status in a German paediatric cohort: A cross-sectional analysis of the LIFE Child data. *Optometry and Contact Lenses*. 2021.

Content

Introduction and Motivation 4

Aims 8

Background 9

Refractive development in infants and children 9

Eye-growth and axial length 12

Methods 15

Study population 15

Measurements 15

Statistical analysis 16

Cumulative part 17

Refractive status in a German paediatric cohort: A cross-sectional analysis of the LIFE Child data 17

Reference curves for refraction in a German cohort of healthy children and adolescents 37

Longitudinal analysis of axial length growth in a German cohort of healthy children and adolescents 49

Zusammenfassung der Arbeit 58

Summary 58

Conclusion 60

Prospect 61

References 62

Appendix 66

Einreichungserklärung 66

Declaration 67

Wissenschaftliche Beiträge zu den Publikationen 68

Acknowledgments 72

Introduction and Motivation

Digitalisation is ongoing in all aspects of our society and the time spent looking at a screen increases. The Corona crisis has sped up this development and it can be seen that even children aged 4 to 17 years spend more time doing screen activities.[1]

These changes in daily activities have an impact on the development of the eyes. Increased near work and less time spent outdoors leads to an increase of myopia prevalence in children.[2] It has already been shown that the additional screen time or reduction in time spent outdoors due to Corona leads to an increase in myopia prevalence in young children aged 6 to 8 years (Figure 1).[3]

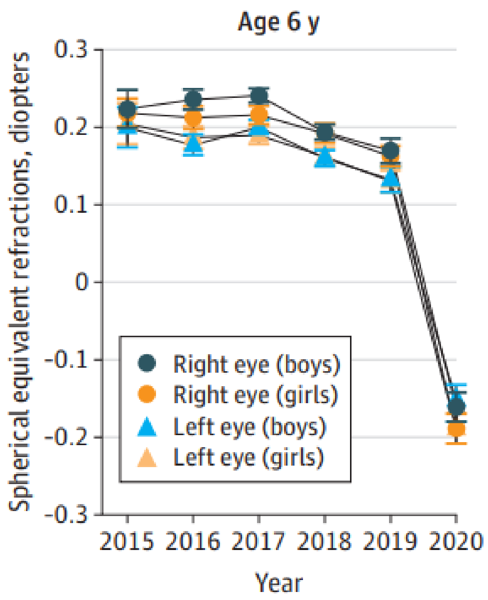

Figure 1: Mean spherical equivalent refraction in 6 year old children; cross-sectional data from 10 primary schools in Feicheng (China) in the years 2015 to 2020; a clear decrease in spherical equivalent can be seen after the strict Lockdown in 2020[3]

The KiGGS study revealed, that myopia prevalence in Germany in the years 2003 to 2006 in the age group 14 to 17 was 20,5% in boys and 29,7 % in girls (Figure 2). However, in this study data was self-reported by the parents and analysis dependent on age groups. The LIFE Child data allows for a more comprehensive insight of myopia prevalence and development in Germany.

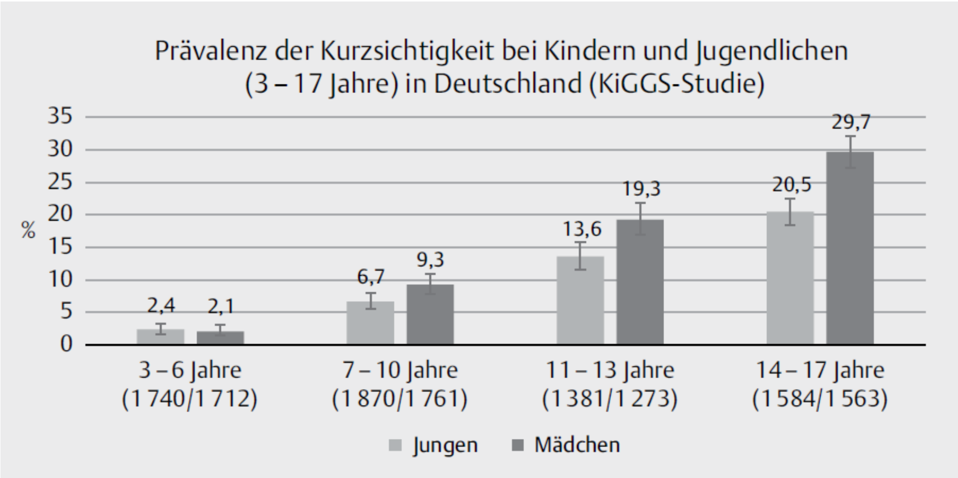

Figure 2: Myopia Prevalence in 3 to 17 year old children in Germany from the KiGGS Study[4]

In East Asian countries the prevalence of myopia and high myopia is much higher compared to Europe.[5] Since myopia is associated with sight-threatening co-morbidities such as retinal detachment[6], myopic maculopathy[7], glaucoma[8] and cataract[9], the aim should be to avoid an increase of myopia prevalence in Europe.

Fortunately methods have been developed to reduce myopia progression. A way to prevent the incidence and progression of myopia is to increase the near work distance, reduce the time spent with near work activities and increase the time spent outdoors (Figure 3).[10]

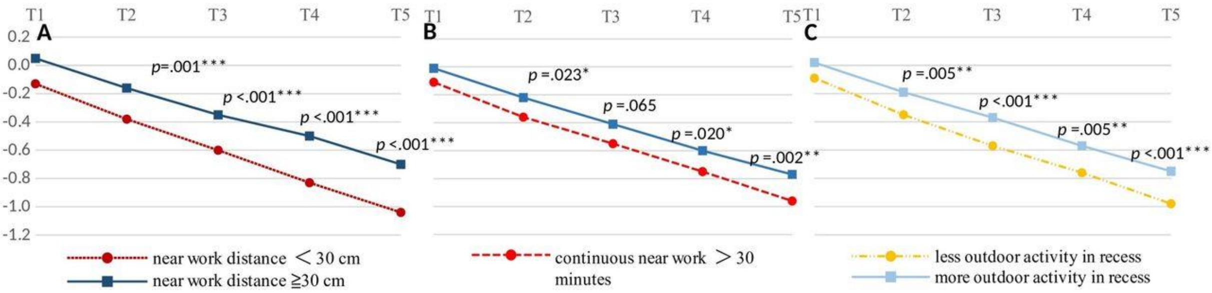

Figure 3: Rates of myopia progression within 2 years in Chinese School children aged 9 to 11 years in respect to near work distance, discontinued near work time and time spent outdoors. Near work distance ≥ 30, discontinued near work every 30 minutes and more outdoor activity are associated with a smaller amount of myopia progression.[10]

If myopia has already been diagnosed, myopia progression can be slowed down with low-dosed atropine eyedrops daily or contact lenses, of which is orthokeratology most successful.[11] Orthokeratology is a technique in which contact lenses are worn over night and change the shape of the epithelium of the cornea. This leads to clear vision during the day without spectacles or contact lenses. A therapy with Atropine eye drops or Orthokeratology can not only reduce the progression of myopia but also the rate of elongation of the eye (Figure 4).[12]

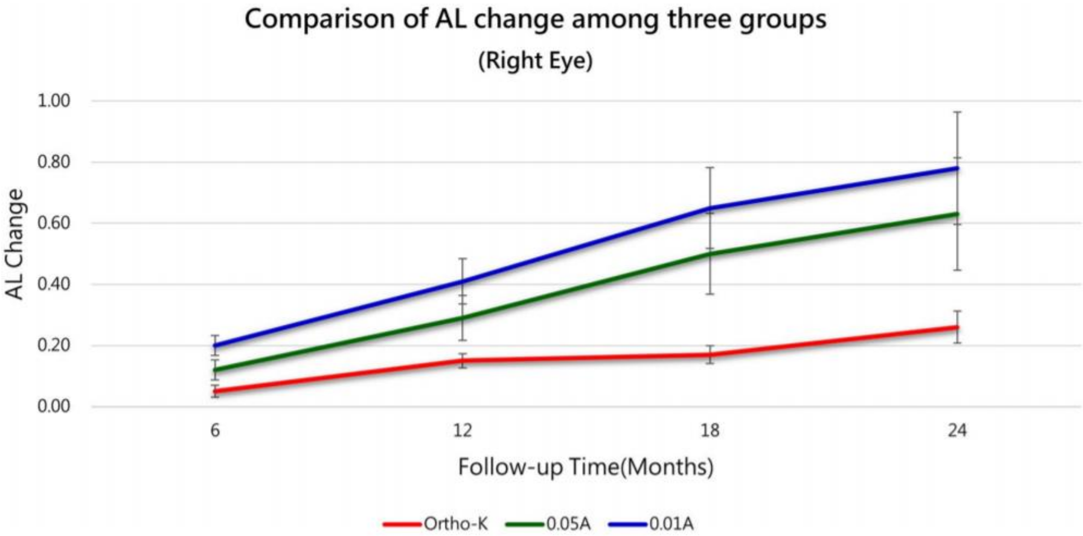

Figure 4: Monocular change in axial length within 2 years of intervention with Ortho-K (red), Atropine 0.05% (green) and Atropine 0.01 % (blue). Axial length increased in all three cohorts but in the Ortho-K group an obvious suppression of axial length growth compared to Atropine was seen.[13]

It is important that children at risk to develop myopia are detected early and parents are educated in ways to prevent myopia progression.

The sensibilisation to these topics can be achieved through the paediatricians, who are the primary consultants to the parents regarding the health of their children. The professional association of paediatricians in Germany recommends in their screening concept paed.plus to check children's eyes with the vision screener for amblyopia and refraction.[14] The next step would be to observe refractive development using centile curves of refraction. The use of these curves is already common in the observation of weight and height in children (Figure 5).

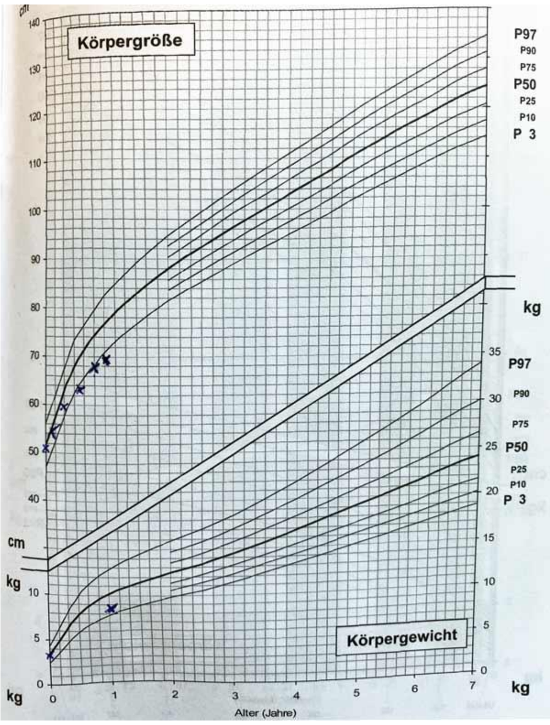

Figure 5: A page of the booklet of child's medical records, which is handed out to the parents in Germany after birth to monitor the child's development. Height and weight are monitored with centile curves.

Optometrists are contact persons for children who already have glasses. They can also educate parents in ways to slow myopia progression, such as Atropine eye drops and Orthokeratology. Currently new devices in Optometric practices are introduced to measure eye length (axial length). Myopia is associated with increased axial length. Increase in axial length can even be observed before the onset of myopia.[15]

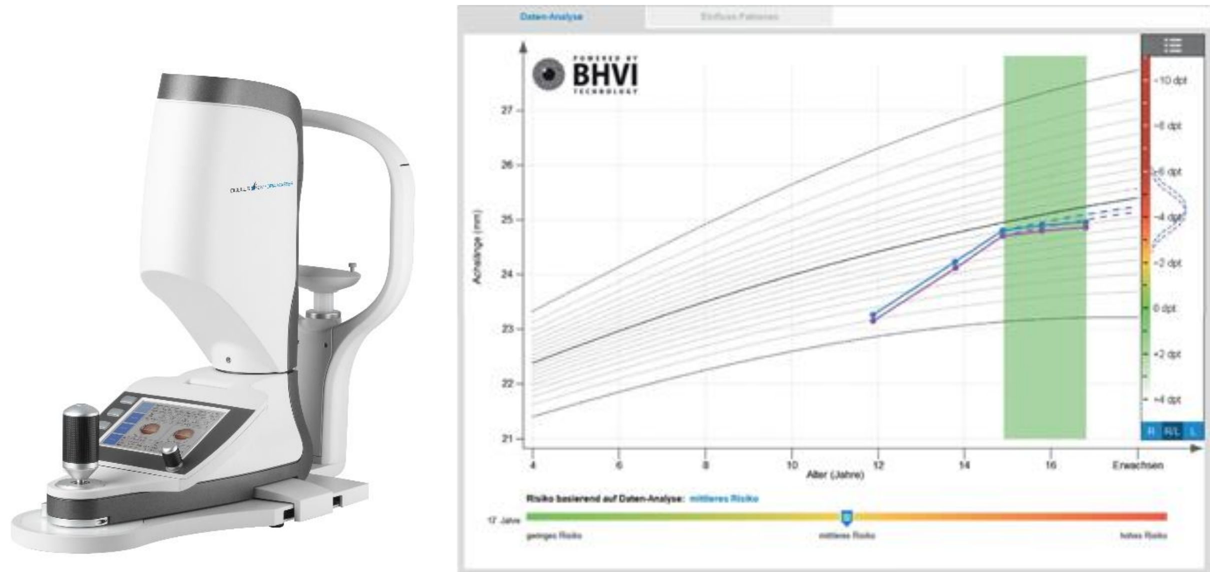

Figure 6: Myopia Master (Oculus Optikgeräte) on the left and the record that is created throughout several visits on the right. Development of axial length is monitored with the use of centile curves.

The measurement of axial length is very accurate[16], whereas the accuracy of refraction in children strongly depends on the control of accommodation.[17] Therefore the new approach to monitor children's eye development not with refraction alone but with refraction and measurements of axial length is promising. In order to analyse data correctly, a good database for the centile curves is required. Currently the centile curves in the database of the Myopia Master (Oculus Optikgeräte GmbH, Wetzlar, Germany) are based on a study by Tidemann et al. In this study data from 6, 9 and 15 year old children from several study sites in Europe were analysed. For the age groups in between the centile curves are estimated in the OCULUS Myopia Master database.

Aims

The present situation requires more data on the current status of refraction and axial length in children in Germany. Therefore, this thesis aims to:

1) Define the current status of myopia prevalence in children in Germany detailed for every year of age.
   Hypothesis: Myopia prevalence in the LIFE Child study is comparable to other German and European paediatric cohorts.
2) Generate percentiles for refraction over age to improve analysis of refractive data in children in paediatric practices.
   Hypothesis: The development of refractive error in China diverges from LIFE Child reference group around the age of school enrollment, and the difference is larger for the lower centiles.
3) Generate percentiles for axial length over age to improve analysis of axial length data in children in Optometric practices and Ophthalmologists.
   Hypothesis: Eye length can be reliably measured, and reference curves for eye length development can be used to identify children with high risk for myopia.

Background

Once a baby is born it has its first contact with the visual world. This is the commencement of visual development. At birth infants are able to fixate faces at a close distance.[18,19] Visual abilities then improve during the first decade of life.[20,21] At the same time the eye grows.[22]

The infantile eye is commonly mildly hyperopic and with elongation of the eye and refractive changes in cornea and lens the **emmetropization process** commences. Increasing axial length leads to a myopic shift in the eye. At the same time the cornea and predominantly the lens lose refractive power, which compensates the myopic shift.[23] This fine-tuned process should lead to emmetropia, a state in which no glasses are required.

Refractive development in infants and children

0 to 6 years: Emmetropization

At birth most infants are hyperopic. When measuring refraction at one month there is a huge standard deviation, showing that there are enormous individual differences at birth.[24] At this age the mean refraction is 2.0 D.[25,26] Figure 7 shows the distribution of refraction at birth up to 4 years of age.

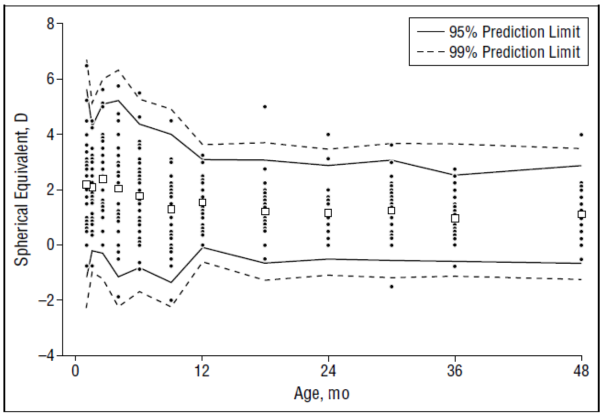

Figure 7: Distribution of the spherical equivalent in 12 age groups from 0 to 48 months of age. The prediction limits show that the standard deviation of the spherical equivalent is larger at birth compared to children aged 12 months. This development is part of the emmetropisation process.[25]

During the first months of life there is a huge elongation of the eye.[24] If the eye was only growing without changing the optics, infants would become more and more myopic with the growing eye. An elongation of the eye of 1mm would cause a change in refraction of -3.0 D. But in the growing eye there is also a stretching of the cornea and the lens, causing a reduction in optical power. Growth of the eye is a very fine-tuned process, where the changes in lens power, corneal power and axial length are coordinated.[27] Interestingly this process is related to the initial refractive error of the infant. More hyperopic children show a higher increase in axial length during the first year of life, thus leading to a refraction closer to emmetropia, still being mildly hyperopic.[22,25]

Mutti et al. have shown, that the emmetropization process seems to fail, if there is initial hyperopia above +5.0 D or initially emmetropia or myopia. Children with high hyperopias tend to continue being hyperopic. Emmetropic and myopic infants however, became myopic or stayed myopic between the age of three and nine months.[22]

By the age of three years the mean refraction is +0.75 D with a much smaller standard deviation, compared to the standard deviation at birth.[26] This shows that the emmetropization process has lead predominantly to a state in which no glasses are required for sharp vision. If ametropia occurs, hyperopia is more common in children than myopia.

The emmetropization process continues up to the age of six years and the prevalence of myopia is generally low. At six years, being mildly hyperopic of at least +0.75 D is a protective factor for myopia.[28]

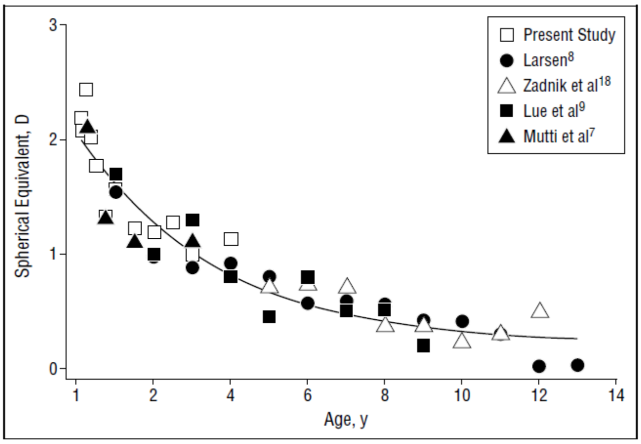

Figure 4. Mean spherical equivalents plotted in Figure 1 and those reported in Mutti et al,[7] Larsen,[8] Lue et al,[9] and Zadnik et al.[18] The smooth curve is a simple exponential function (time constant, 3.6 years) fit to all of the plotted points. D indicates diopters.

Figure 8: Development of the mean spherical equivalent from 1 to 13 years of age in Norway (circle) and the USA (all other studies). In younger children the mean spherical equivalent is mildly hyperopic and becomes less hyperopic with increasing age.[25]

After 6 years of age: trend towards myopia

After the age of six years the distribution of refraction is dependent on the population studied. Widely there is a tendency of increased incidence and prevalence of myopia. However, in some countries like Australia and Nepal there is even further emmetropization after the age of 6. For

European countries a mild increase in myopia prevalence is observed with increasing age, while the incidence, prevalence and progression of myopia in many Asian countries after the age of six is rocketing.[26] A mild reduction of refraction at this age may still be normal as with increasing age a lower hyperopia seems to be protective for myopia. Where for a six year old child a refraction of +0.75 D is protective for myopia, +0.5 D is protective in seven and eight year old children, +0.25 D in nine and ten year old children and even emmetropia is protective, if the child is at least 11 years old.[28]

For Germany the prevalence of myopia in the age group 3 – 6 years is 2.4% for boys and 2.1% for girls. An increase of the prevalence can already be seen in the age group 6 to 10 year old children with 6.7% and 9.3% for boys and girls, respectively. In the oldest age group studied, 14 to 17 years, the prevalence was 20.5% for boys and 29.7% for girls (Figure 2).[4] This data by the KIGGS Study supports, that myopia development in Germany starts as early as six years and then continues until adulthood.

A way to show the development of refraction in a cohort, which shows not only myopia prevalence but also the prevalence of high myopia and hyperopia is by using centile curves. Figure 9 shows centile curves from a cohort of children in Guangzhou in China. The trend towards increasing prevalence of myopia and high myopia with increasing age can clearly be seen. To understand the differences of refractive development between different populations it would be interesting to compare centile curves of refraction.

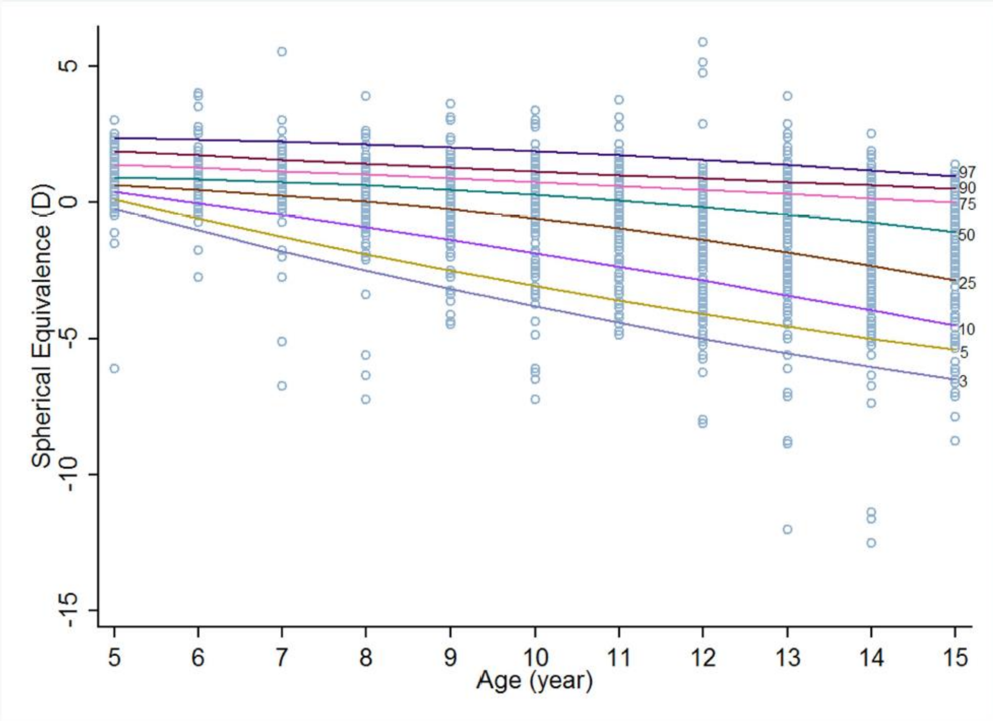

Figure 9: Percentile curves for Chines boys aged 5 to 15 years. In China a clear trend towards a myopic development with increasing age can be seen. [29]

Eye-growth and axial length

Axial length growth due to developmental elongation of the eye

At birth the eye is approximately 17 mm long and grows to a size of about 23 mm in adolescence.[27] The elongation is biggest during the first year of life, with decreasing growth rates towards the end of the first year. At 12 months the axial length is about 20 mm.[22,24] At three years the emmetropic eye is almost 22 mm long, showing that the rate of axial elongation has further decreased.[30]

6 to 9 year old emmetropes in Singapore had an average axial length of 23 mm.[23] A more detailed study from America measured an axial length at 6 years of 22.33 mm for girls and 22.82mm for boys which increased by the age of 9 to 23.02 mm and 23.40mm, respectively. At 14 the axial length was 23.48 for girls and 23.69 for boys. Towards the end of the observed period (14 years) only marginal changes of axial length were measured.[31] Identically to Zadnik et al. Hashemi et al. found that axial length in Iran is gender-depended with longer eyes in boys. After the age of 14 only little changes were observed in both groups and may be due to myopia development.[32]

This shows, that axial length seems to stabilize at this age, possibly reaching its end point. However, if the average axial elongation in a population is studied, it cannot be distinguished between growth-related and myopia-related axial elongation. There are only few studies, which measured axial length in emmetropes only, thus marking the growth-related end point of axial length. The axial length of 22 emmetropic Australian adults aged 18 to 36 years was 23.0 mm.[33] In India axial length in 102 emmetropes aged 14 to 60 was 23.52 mm.[34] In emmetropic Korean adults axial length was 23.41 mm[35] and in emmetropic Dutch adults axial length was 23.30mm[36]. Thus, the emmetropic end point of axial elongation appears to be around 23.0 mm to 23.5 mm.

It could also be shown, that axial length is correlated to body height and weight, which has no correlation with myopia.[37,38]

Axial length growth due to myopia

Jin et al. describe the axial length growth as a logarithmic function, which asymptotes towards an end point. Their end point observed was 24.35 mm at 15 years.[39] This data is for a cohort of Chinese children and children of all refractive states were included. As at this age most of the children are myopic, this shows not the emmetropic end point, but axial elongation due to myopia development.[5] This shows that axial length is depended on the ethnicity and region when all refractive states are included. In this case increased axial length is a sign of a high prevalence of myopia in a cohort.

In order to compare axial length between several ethnicities in different age groups centile curves of axial length may be a useful tool. Tidemann et al. have created such curves for European children aged 6, 9 and 15 years old (Figure 10). Their data of children aged 6 and 9 are derived from a Dutch study and the data of 15 year of children from a British study.

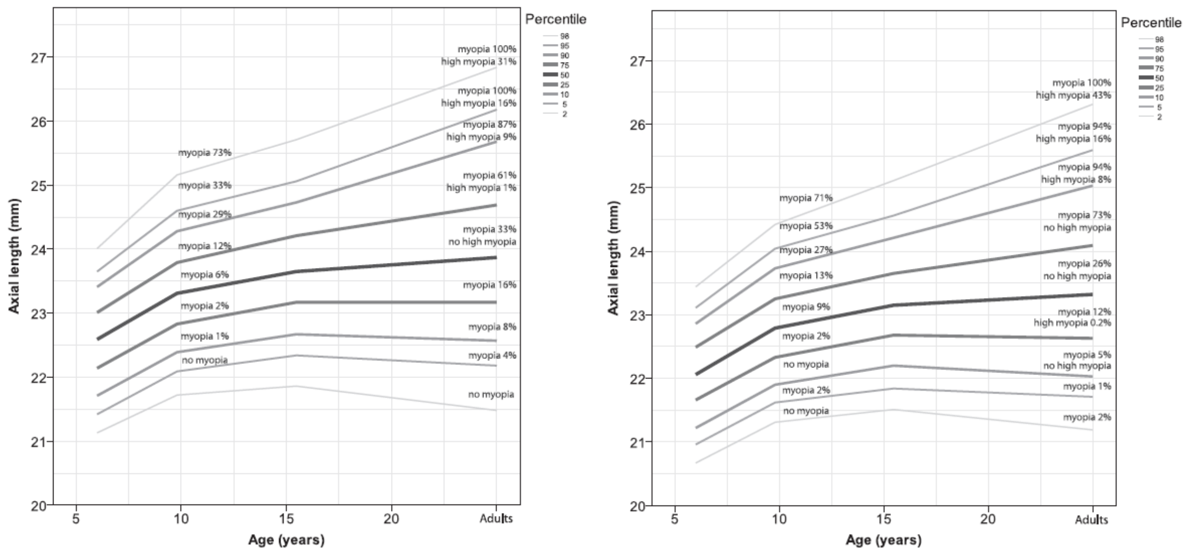

Figure 10: Centiles of axial length in Europe created from data at age 6, 9, 15 and in adults (males on the left and females on the right)[36]

Sanz Diez et al. have created similar curves for a cohort from China with continuous data from age 5 to 15 (Figure 11). Both, Tidemann et al. and Sanz Diez et al. have also calculated the prevalence of myopia for each centile of axial length, which increases with increasing axial length. More detailed data on axial length in children in Europe would be desirable for comparison to Chinese data.

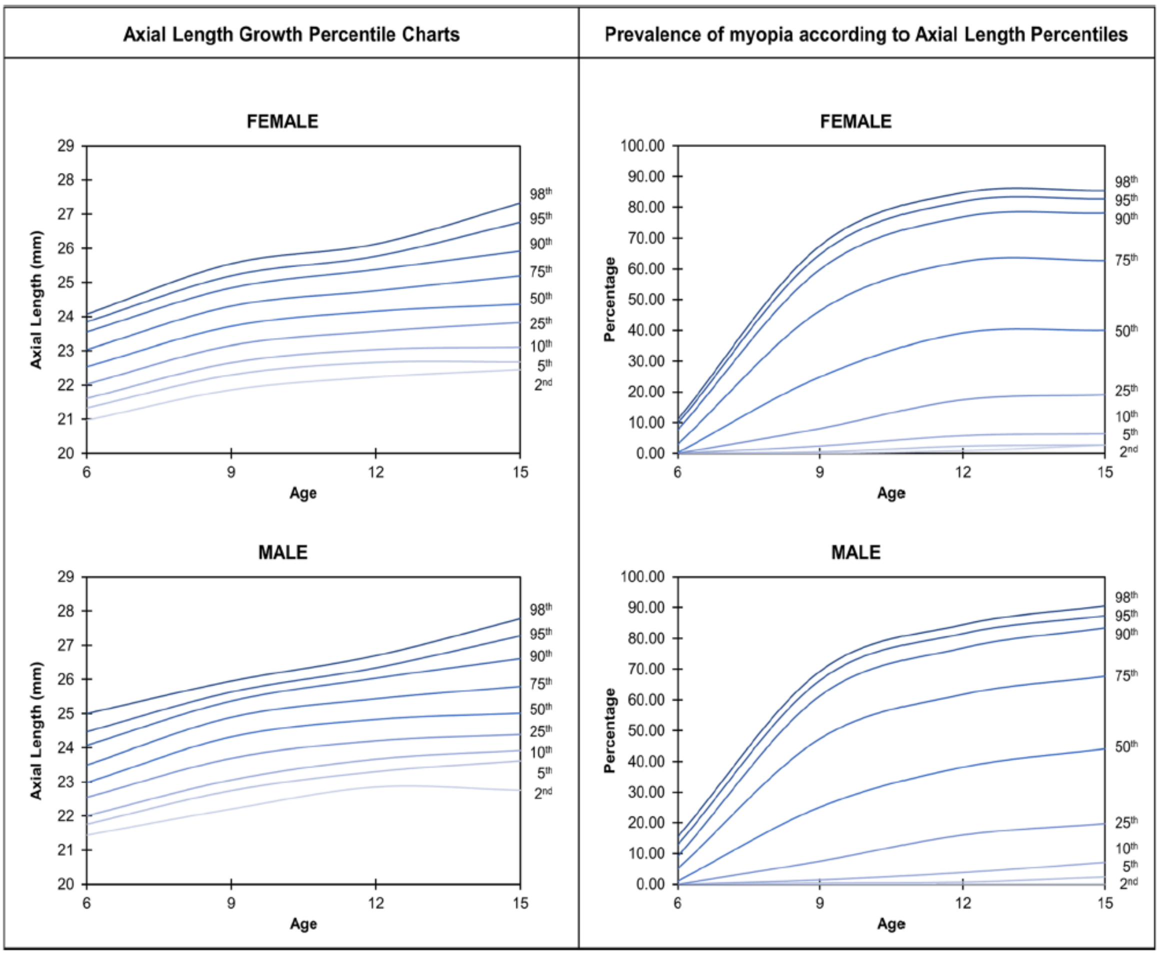

Figure 11: Centile curves of axial length of children aged 5 to 15 years in China on the left and the respective prevalence of myopia for each centile on the right.[40]

Methods

Study population

For all analysis the LIFE Child data were used. LIFE Child is a study in which healthy child development is monitored. The study population is divided into three interrelated cohorts: the birth cohort, the health cohort and the obesity cohort. It is a cross-sectional and longitudinal study and aims to understand a wide range of factors influencing health and growth in children. Study data is representative with a bias towards higher educational and socioeconomic status. Data is collected in Leipzig in Germany.[41] Refraction and biometry of the eye are carried out from the age of three. Participants are invited annually for continuous measurements. Collection of the relevant data was between January 2014 and May 2018, so that a maximum observation period of 4 years was analysed.

Measurements

Autorefraction without Cycloplegia was carried out with the Zeiss i.Profiler plus (Carl Zeiss Vision GmbH, Aalen, Germany). In order to relax accommodation the focus target was defocussed initially (fogging). The i.Profiler plus is an Aberrometer measuring the wavefront aberrations. The refractive error was calculated at a pupil diameter of 3mm and a vertex distance of 12 mm. In order to maximize pupil size throughout the measurements the room light was switched off and the window blinds were closed. Biometry was measured with the LENSTAR (Haag-Streit, Könitz, Switzerland). Both, Aberrometry and Biometry were carried out three times in each eye. Visual acuity without and if applicable with correction were determined by and optometrist using logMAR charts (ZEISS i.Polatest, Carl Zeiss Vision GmbH, Aalen, Germany) at 6 m distance and ambient room lighting. In addition parents or, in older children, the participants themselves completed a questionnaire and gave information on the history of eye surgeries, eye diseases and spectacle use.

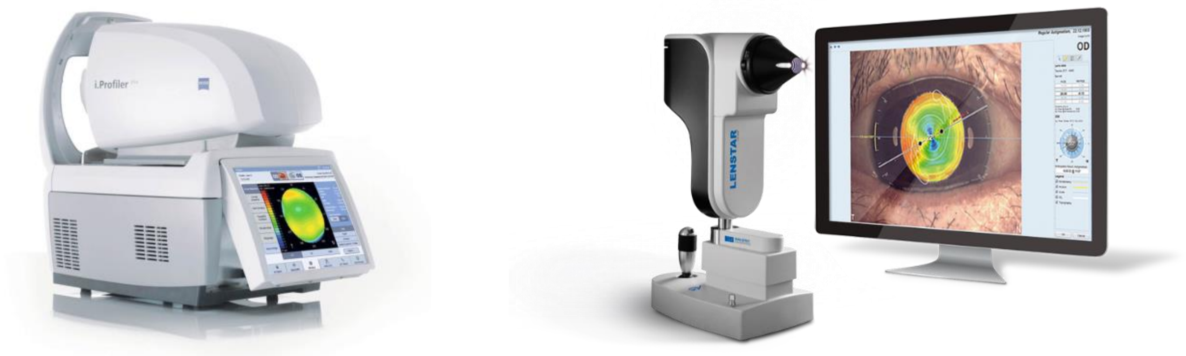

Figure 12: Zeiss i.Profiler plus (Carl Zeiss Vision GmbH, Aalen, Germany) on the left and the LENSTAR (Haag-Streit, Könitz, Switzerland) on the right.

Statistical analysis

Of the three measurements taken by the i.Profiler plus at each visit the spherical equivalent (SE = sphere + ½ cylinder) of the right eye was calculated. The median was used for reference interval calculation. Also, for axial length the median out of three measurements of the right eye was used.

The data for refraction development and axial length as a function of age were statistically analysed as a continuous function, as recommended by the WHO.[42] In comparison to age intervals for which the centiles could be calculated this method results in smoother curves and provides better comparableness. For calculation of the centile curves the GAMLSS model was applied. The software R, by the R foundation, with the additional package “gamlss” was used.

For obtaining growth curves only one visit of each participant and only one member of each family can be analysed. Since this procedure would lead to only a small number of data, especially at the older age groups, a method by Vogel et al. was used to generate reference intervals from unbalanced, interrelated data. Thereby a resampling technique is used. Reference curves are calculated several times with subsamples of the cohort. For each calculation 75% of the families are sampled. Then in a second step only one measurement out of all available measurements of each family is sampled. By using sampling weights each person has the same probability to be selected. Reference curves are then calculated from this subsample. This is done 1000 times. The final result is the mean of these 1000 single estimated values.[43]

Cumulative part

Refractive status in a German paediatric cohort: A cross-sectional analysis of the LIFE Child data

Publication accepted 03.03.2021 in Optometry and Contact lenses

Refraktionsstatus deutscher Kinder in der LIFE Child Studie

Refractive status in a German pediatric cohort: A cross-sectional analysis of the LIFE Child data

Manuela Brandt[1], Christof Meigen[1], Carolin Truckenbrod[1*], Mandy Vogel[1,2], Tanja Poulain[1,2], Anne Jurkutat[1], Franziska G. Rauscher[1,3], Wieland Kiess[1,2], Siegfried Wahl[4,5]

[1] LIFE Leipzig Research Center for Civilization Diseases, Leipzig University, Philipp-Rosenthal-Strasse 27, 04103 Leipzig, Germany
[2] Department of Women and Child Health, University Hospital for Children and Adolescents and Center for Pediatric Research, Leipzig University, Liebigstrasse 20a, 04103 Leipzig, Germany
[3] Institute for Medical Informatics, Statistics and Epidemiology, Leipzig University, Haertelstrasse 16-18, 04107 Leipzig, Germany
[4] Institute for Ophthalmic Research, Eberhard Karls University Tübingen, Elfriede-Aulhorn-Straße 7, 72076 Tübingen, Germany
[5] Carl Zeiss Vision International GmbH, Elfriede-Aulhorn-Straße 7, 72076 Tübingen, Germany

* Corresponding author
E-Mail: carolin.truckenbrod@t-online.de
Carolin Truckenbrod
Johannisplatz 19
04103 Leipzig

Manuela Brandt	manuela.brandt@medizin.uni-leipzig.de
Christof Meigen	cmeigen@medizin.uni-leipzig.de
Dr. Mandy Vogel	mvogel@medizin.uni-leipzig.de
Dr. Tanja Poulain	tpoulain@medizin.uni-leipzig.de
Dr. Anne Jurkutat	ajurkutat@medizin.uni-leipzig.de
Dr. Franziska G. Rauscher	Franziska.Rauscher@medizin.uni-leipzig.de
Prof. Dr. Wieland Kiess	Wieland.Kiess@medizin.uni-leipzig.de
Prof. Dr. Siegfried Wahl	siegfried.wahl@zeiss.com

Interessenkonflikt

Siegfried Wahl ist bezahlter Angestellter der Firma Carl Zeiss Vision International GmbH.

S. Wahl is an employee of Carl Zeiss Vision International GmbH, however, none of the authors have any financial or conflicting interests concerning the content of this research which was conducted following the rules of neutral scientific practice.

Abstract

Aim: Current prevalence rates of myopia in children and adolescents vary all over the world, with especially high prevalence rates in East Asian countries. The objective of this study was to describe the refractive status in children and adolescents growing up in Germany.

Methods: Non-cycloplegic refractive status of children of the LIFE Child study in Leipzig, Germany, was measured by wavefront-based autorefraction in 1934 subjects (925 girls / 1009 boys), aged 3 to 16 years (mean = 9.05 ± 3.91). Myopia was defined as spherical equivalent refractive error (SE) $\leq$ -0.75 diopters (D), emmetropia as -0.75 D $>$ SE $<$ +0.75 D, hyperopia as SE $\geq$ +0.75 D and astigmatism as cylinder $\leq$ -0.75 D. Anisometropia was defined as a difference of $\geq$ 1.0 D in the SE between the two eyes.

Results: Analysis revealed that refractive error became more myopic with older age ($b = -0.08$, $p < 0.001$), with an observed prevalence of myopia of 27% in 16-year-old children (4% in 3-year-olds). The true prevalence of myopia might be lower as non-cycloplegic measurements might overestimate refractive error in myopes and underestimate refractive error in hyperopes which in turn may overestimate the prevalence of myopia. The prevalence of anisometropia also increased with growing age (OR = 1.14, observed prevalence in 3- versus 16-year-olds = 2.3% and 8.1%, respectively). The prevalence of astigmatism was 11.8 %.

Conclusions: Myopia prevalence in German children aged 3 to 16 years is around or even less than 10%, taking into consideration that measurements were carried out without cycloplegia. Our results are comparable to other European paediatric studies. In comparison to East-Asian countries myopia prevalence and thus the risk for eye diseases related to high myopia is much lower in Germany.

Abstrakt

Zweck: Die Häufigkeit der Myopie ist weltweit unterschiedlich, mit besonders hohen Prävalenzen in Ostasiatischen Ländern. Das Ziel der Studie ist es, den refraktiven Status von Kindern und Jugendlichen in Deutschland zu beschreiben.

Methoden: Der Refraktionsstatus von 1934 Studienteilnehmern (925 Mädchen / 1009 Jungen) der LIFE Child Studie (Leipzig, Deutschland) im Alter von 3 bis 16 Jahren (Mittelwert = 9,05 ± 3,91) wurde mit nicht-zykloplegischer wellenfrontbasierter Autorefraktion gemessen. Die Einteilung des sphärischen Äquivalents (SÄ) war ≤ -0,75 Dioptrien (dpt) für Myopie, -0,75 D > SÄ < +0,75 dpt für Emmetropie und SÄ ≥ +0,75 dpt für Hyperopie. Der Astigmatismus wurde als Zylinder ≤ -0,75 dpt eingeteilt. Anisometropie wurde als eine Differenz des SÄ ≥ 1,0 dpt zwischen beiden Augen definiert.

Ergebnisse: Die Analyse ergab, dass der Refraktionsfehler für ältere Kinder stärker myop war (b = -0.08, $p < 0.001$), mit einer beobachteten Prävalenz der Myopie von 27% bei 16-jährigen Kinder (4 % bei 3-jährigen Kindern). Da Messungen ohne Zykloplegie dazu tendieren den Refraktionsfehler bei Myopen zu überschätzen und bei Hyperopen zu unterschätzen und somit die Prävalenz der Myopie zu überschätzen, könnte die tatsächliche Prävalenz der Myopie sogar geringer sein. Auch die Prävalenz der Anisometropie stieg mit höherem Alter (OR = 1.14, beobachtete Prävalenz bei 3-jährigen = 2,3% und 16-jährigen 8,1 %). Die Prävalenz von Astigmatismus lag bei 11,8%.

Fazit: Die durchschnittliche Prävalenz der Myopie bei Deutschen Kindern zwischen 3 und 16 Jahren ist circa 10% oder sogar niedriger, wenn man bedenkt, dass unsere Messungen ohne Zykloplegie durchgeführt wurden. Unsere Ergebnisse sind vergleichbar zu denen anderer pädiatrischer Studien in Europa. Im Vergleich zu Ostasiatischen Ländern ist die Myopieprävalenz, und somit das Risiko für myopiebedingte Augenerkrankungen, in Deutschland viel geringer.

Introduction

Uncorrected refractive error is the most common cause for moderate or severe distance vision impairment worldwide and the second leading cause of blindness [1]. Myopia in older adults is related to an elevated risk for glaucoma [2], myopic maculopathy [3] and cataract [4]. High myopia increases the risk of pathologic ocular changes, such as retinal detachment [5]. Hyperopia, in contrast, is associated with higher proportions of strabismus and anisometropia in children [6]. Both are common causes of amblyopia.

Besides, visual impairment due to uncorrected myopia causes massive economic burdens worldwide. Naidoo et al. [7] estimated the global potential productivity loss from uncorrected myopia at US$ 244 billion. Moreover, Holden [8] predicted that in 2050, 49.8 % of the world population will be myopic and 9.8 % will have high myopia, respectively. Consequently, the already high costs might increase steadily.

Comparison of different data regarding the prevalence of myopia in childhood is difficult due to different age groups, varied refractive measurement methods (for example, the use of cycloplegia) and variability in the definition of myopia. Current prevalence rates of myopia vary all over the world. In children and adolescents aged 5 to 15 years, who underwent cycloplegic autorefractometry, myopia (SE ≤ -0.5 D) was observed in 2.6 % in Iran [9], whereas in China [10], 36 % of participants were reported to be myopic.

So far, limited data have been published for Europe and notably Germany. In Poland [11], 13.3 % of participants aged 6 to 18 years were reported to be myopic whereas children and adolescents between 12 and 13 years living in Sweden [12] showed prevalence rates of 49.7 %. In the UK, the prevalence of myopia in 6- to 20-year-old children was reported to range between 2% in the youngest and 19% in the oldest children [13]. Käsmann-Kellner et al. [14] published 1998 myopia prevalence rates of 8 % in German kindergarten children using retinoscopy without cycloplegia. Nearly 20 years later, the KiGGS study, a nationwide, population-based health survey in Germany, found a prevalence of myopia of 13.3 % in children and adolescents aged 3 to 17 years [15]. However, in this survey, status of myopia and the use of spectacles were reported by parents. It needs to be taken into account that parents are not always able to distinguish between myopia and hyperopia. The result of the KiGGS study is similar to the findings of another German study, which reported a myopia prevalence rate of 11.9 % in children and adolescents aged 2 to 17 years [16]. The authors used data about refractive correction based on self- or parent-reported information of prescribed spectacles. However, also children without spectacles might have ametropia. Furthermore, ophthalmologists might differ in their criteria or cut-offs for prescribing spectacles.

The present study aimed to describe the distribution of refractive status depending on age and sex based on objective wavefront-based autorefraction measurements in a large cohort of German children and adolescents.

Materials and Methods

Participants

Data were collected during the period of January 2014 to May 2018 in the LIFE Child study center in Leipzig, Germany. The LIFE Child study (clinical trial number NCT02550236) is a longitudinal childhood cohort study aiming to investigate healthy child development and the development of civilization diseases [17,18]. Participants mainly originate from the city of Leipzig and surrounding areas are recruited via advertisement at different institutions, such as schools and public health centers between birth and 18 years of age. All families interested in the study are invited to participate voluntarily. Children suffering from any chronic, chromosomal, and syndromal diseases are excluded. Subsequent visits are scheduled every year.

Informed written consent was provided by all parents before the inclusion of their children in the study. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Leipzig (Reg. No. 264/10-ek).

For the present study, baseline measurements of 3- to 16-year-old children and adolescents (n = 1934) were analyzed.

Examination procedures

Noncycloplegic refractive status of each eye (3 mm pupil diameter and 12 mm vertex distance) was measured three times using a wavefront-based autorefractor (ZEISS i.Profiler® plus, Carl Zeiss Vision GmbH, Aalen, Germany). Uncorrected distance monocular logMAR visual acuity was determined according to a detailed standard operating procedure by a team of three experienced optometrists using logMAR charts (ZEISS i.Polatest®, Carl Zeiss Vision GmbH, Aalen, Germany) at 6 m distance. Ambient room lighting and single line letters were used. For children who were not able to read letters, line or single Kolt-test optotypes were presented. A line was passed, if three out of five optotypes were read correctly. At every eye examination, past or present eye diseases were documented. The measurement of cycloplegic refractive status was rejected by the Ethics Committee and, therefore, not applied in this study.

Definition of refractive errors

Refractive data were converted to the spherical equivalent (SE = sphere + cylinder/2). For each child, we selected the median SE measurement of the three measurements and used the respective SE and cylinder values for all further analyses. In young population non-cycloplegic autorefraction might show a myopic shift in refractive error due to excessive residual accommodation [19]. This bias might lead to an overestimation of myopia or an underestimation of hyperopia. Based on grouping for non-cycloplegic refraction in a systematic review by Hashemi [20] and a recommendation by the International Myopia Institute [21], we used the following definition for refractive error: myopia: SE ≤ -0.75 diopters (D); emmetropia: -0.75 D > SE < +0.75 D; hyperopia: SE ≥ +0.75 D and astigmatism ≤ -0.75 D. Anisometropia was defined as a difference of ≥ 1.0 D in the SE between the two eyes [22].

Data analysis

All analyses were conducted using R, version 3.3.4. The Kolmogorov-Smirnov-Test was used to test the difference of the distributions of the SE of left and right eyes, as well as to test whether the SE was normally distributed. Spearman correlation analysis was conducted to assess the relationship between SE or anisometropia and age and Mann-Whitney-U-Test was performed to investigate gender differences. Logistic regression was used to examine odds ratios (OR) to assess associations between the prevalence of myopia, emmetropia, hyperopia or anisometropia and age. Possible relations between prevalence of refractive status and gender were tested by χ^2 tests. The significance level alpha was set to 0.05. Detailed analyses were carried out on the right eye for all participants.

Results

Myopia, emmetropia and hyperopia

The sample consisted of 1934 children and adolescents (925 girls, 1009 boys, mean age = 9.1 years; SD = 3.9). Information on the socio-economic status of the family, which were self-reported by the parents, was available in 1833 children (95%). Of these children, 11% belonged to the low, 57% to the middle, and 33% to the high social stratum. Compared to a large representative sample, this distribution indicated a slight underrepresentation of the low social stratum [23].

The mean SE of all 1934 children and adolescents was -0.03 D (SD = 1.13 D) for the right eyes and -0.04 D (SD = 1.13 D) for the left eyes. There was no significant difference in the distribution of SE between left and right eyes (p = 0.95). For more accessible illustration, the following findings describe right eyes only.

The SE of all children and adolescents, ranging from -7.36 D to +9.05 D, was not normally distributed (p < 0.0001). There were more individuals with a SE above the mean than below (1044 vs. 890 individuals, see Fig 1). Overall, in 79.8 % of the children and adolescents emmetropia was found. Myopia was prevalent in 10.8 % (mean SE: -2.06 D ± 1.43 D) and hyperopia in 9.4 % (mean SE: +1.82 D ± 1.46 D). The prevalence rates of refractive status per year of age are presented in Table 1. Our data showed a higher prevalence of myopia (OR = 1.24, p < 0.0001) and a lower prevalence of hyperopia (OR = 0.90, p < 0.0001) with older age. The prevalence of emmetropia was also lower with older age (OR = 0.93, p < 0.0001, see Fig 2). At the age of 3 years, 4.0 % of the participants were myopic, 78.2 %

were emmetropic, and 17.8 % were hyperopic. At the age of 16 years, in contrast, 27.0 % were myopic, 67.6 % were emmetropic, and 5.4 % were hyperopic. A gender difference in the prevalence of myopia, emmetropia and hyperopia was not observed (χ^2 = 0.70, p = 0.71). Also, the distribution of myopia, emmetropia, and hyperopia did not differ significantly in children from the low, middle, or high social stratum (χ^2 = 0.70, p = 2.70, p = 0.61).

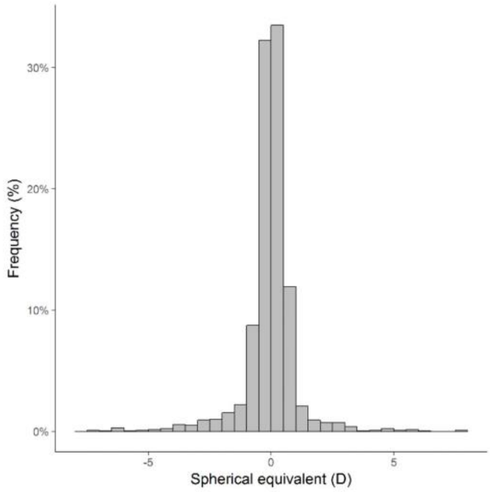

Figure 1: Refractive error distribution in the total population (n = 1934) expressed as spherical equivalent

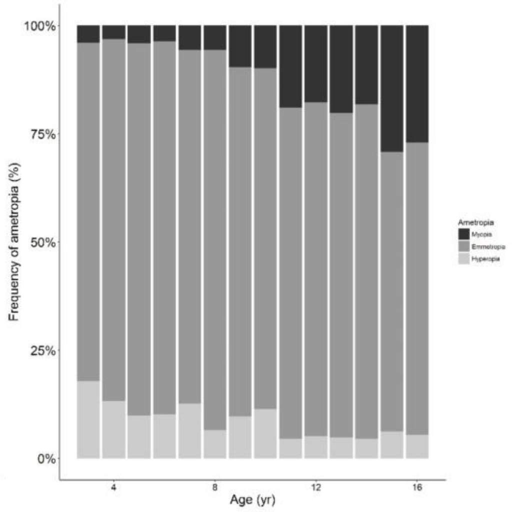

Figure 2: Prevalence of emmetropia, myopia and hyperopia in relation to age

Table 1. Prevalence of myopia, emmetropia, hyperopia, anisometropia and astigmatism among children of 3 to 16 years of age, stratified by age.

Age (yr)	Participants (n)	Myopia (%)	Emmetropia (%)	Hyperopia (%)	Anisometropia (%)	Astigmatism (%)
		SE ≤ -0.75 D	-0.75 D > SE ≤ +0.5 D	SE ≥ +0.5 D	difference of SE ≥ 1.0 D	≤ -0.75 D
3	174	4.0	78.2	17.8	2.3	10.9
4	226	3.0	83.6	13.3	2.2	15.6
5	171	4.0	86.0	9.9	2.9	9.9
6	167	3.5	86.2	10.2	1.8	10.2
7	126	5.6	81.7	12.7	2.4	9.5
8	124	5.6	87.9	6.5	0	8.1
9	145	9.7	80.7	9.7	2.1	8.3
10	132	9.8	78.8	11.4	6.1	15.9
11	132	18.9	76.5	4.5	5.3	8.3
12	175	17.7	77.1	5.1	5.1	9.7
13	104	20.2	75.0	4.8	2.9	12.5
14	88	18.2	77.3	4.5	4.5	12.5
15	96	29.2	64.6	6.3	11.5	19.8
16	74	27.0	67.6	5.4	8.1	20.3
Total	1934	10.8	79.8	9.4	3.7	11.8

Fig 3 shows the distribution of SE by age and the respective regression line. There was a small negative correlation between age and SE ($R^2 = 0.14$, $p < 0.0001$). With older age, the average refractive error was more myopic. At the age of 3 years we observed a mean SE of +0.29 D ± 0.69 D whereas at the age of 16 years the mean SE was -0.56 D ± 1.53 D. The mean SE in males was -0.01 D ± 1.14 D and in females -0.06 D ± 1.13 D. However, this difference did not reach significance ($p = 0.38$).

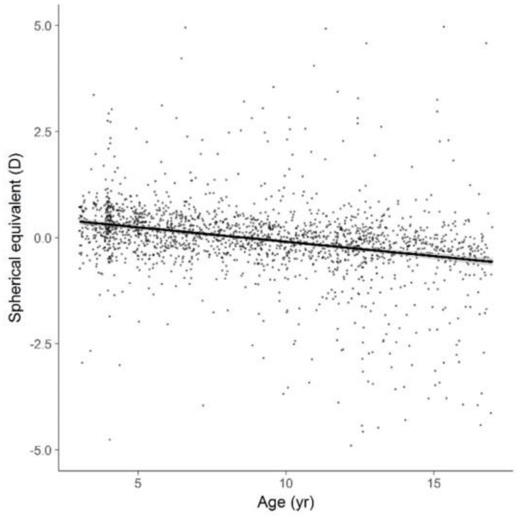

Figure 3: Spherical equivalent as a function of age (r = 0.37, p < 0.0001).

Anisometropia

Anisometropia was present in 3.7 % (n = 71) of the subjects (mean difference in SE between right and left eye: 1.73 D ± 1.13 D, range 1.0 D to 7.38 D). The prevalence of anisometropia did not differ significantly between boys and girls ($\chi^2 = 1.73$, p = 1.0) or between children from different social strata ($\chi^2 = 2.24$, p = 0.33). However, logistic regression showed a significant positive association with increasing age (OR = 1.13, p < 0.0001), i.e., anisometropia was more frequent in older children. At the age of 3 years, 2.3 % of the participants had an anisometropia compared to 8.1 % at the age of 16 years. Of the subjects with anisometropia, 37 % had an anisometropia of less than 1.25 D difference. For the degree of anisometropia we observed no age (p = 0.82) and no sex dependency (p = 0.23). In children with anisometropia, there was no significant difference in the mean of the SE of right and left eyes (p = 0.62), that means neither side was significantly more myopic or hyperopic.

Astigmatism

Astigmatic refractive error was prevalent in 11.8 % (n = 229) of the subjects (mean cyl: -1.34 D ± 0.80 D, range -0.75 D to -4.90 D; see also Table 1). Nearly half of the children and adolescents (48.5 %) with astigmatism had a slight cylinder between -1.0 D and -0.75 D, however, 8.7 % had a cylinder more than -2.5 D.

Discussion

Myopia

The overall prevalence rate of myopia in this study based on non-cycloplegic measurements was shown to increase with growing age from 4% at age 3 to 27% at age 16 (average = 10.8%). For precise assessment of the refractive status, it is usually recommended to apply cycloplegia, since non-cycloplegic measurements tend to yield more myopic values for the sphere in the young population [19]. For ethical reasons, application of cycloplegic agents was not approved in such a large cohort. We are aware that the actual prevalence of myopia is considerably lower than our estimates as a recent published study determined significant differences for the agreement of non-cycloplegic and cycloplegic measurements of wavefront-based autorefraction (same device as in the present study) in German children aged 2 to 15 years [24]. The average difference for the SE resulted in a bias of 0.55 D ($p < 0.001$). Applying this correction to our data yields a corrected estimated prevalence rate of myopia of 6.4 %. Sankaridurg et al. [25] developed a method ("Model B") to determine myopic refractive errors based on a non-cycloplegic measurement of sphere and cylinder, age and uncorrected visual acuity. Likewise the authors analysed an average difference for the SE of 0.63 D in children aged 4 to 15 years living in China. Applying Sankaridurgs et al. model to our data yields a corrected estimated prevalence rate of myopia of 7.1 %. This prevalence rate might still be biased, since the authors conclude that the model might not be appropriate for non-Asian countries and very young populations where hyperopia may be the predominant refractive error. Thus, while the precise prevalence of myopia in German children and adolescents cannot be derived from the current study, the empirical measurements in combination with results from other studies comparing cycloplegic and non-cycloplegic measurements strongly suggest that the true prevalence lies below the reported 10.8 %. This is an important result, especially considering recent trends in China and East Asian countries, showing considerably higher prevalence rates of myopia. Using non-cycloplegic measurements, children at the age of 14 years living Beijing [26] showed myopia prevalences (at least -1.0 D) of 58 % and 62 %, respectively. Using the same cut-off, same-aged participants in the current study showed a prevalence rate of 17 %. This difference might be explained by a complex interaction between increasing educational pressures and increased near work activities and decreased time spent outdoors in China and East Asian countries [27]. Analyzing the influence of these and other factors in the LIFE Child cohort is beyond the scope of this paper.

The measurement-based prevalence of 10.8 % reported for German children is comparable with previous self- or parent-reported information about refractive errors in German children and adolescents [15,16]. It is also in line with those found in other European studies [11,13]. An international quantitative meta-analysis of myopia prevalences in Caucasian European ancestry residing in Europe, America, Australia and New Zealand showed prevalence rates of 1.6 % for 5-year-old, 6.7 % for 10-year-olds, 16.7 % for 15-year-olds and 22.8 % for 18-year-olds children [28]. Children and adolescents aged 7 to 16 years living in Bosnia and Herzegovina [29] as well as Swedish children aged 12 to 13 years [12] showed higher prevalence rates (20.4 % and 49.7 %).

In the current study, no gender differences were observed regarding the prevalence of myopia. This finding is supported by earlier published studies either in Europe [12] or East Asian studies [30]. In contradiction, some European and Asian studies observed a higher prevalence of myopia in females than in males [16,26]. These gender differences might be explained by more near work and less outdoor activities in females vs. males [31].

Furthermore, similar to other European and Asian studies [11,16,30], we observed that with older age not only the prevalence of myopia increases but also the average refractive error becomes more myopic. Parts of this change of refraction reflects the process of emmetropization, which is largely completed by the age of 6 years [32]. However, the situation in China and East Asian countries differs from that in our study. At the age of 16 years, 27.0 % of our participants had myopia and as already mentioned, this frequency is often exceeded in China and East Asian countries where also the prevalence of high myopia is higher. Lam et al. [30] reported that 1.8 % Hong Kong Chinese schoolchildren aged 6 to 12 years had high myopia of more than -6.00 D. In the study by You et al. [26] 4.3 % of Chinese children at the age of 7 to 18 years were high myopic. Consequently, the risk of pathological eye changes increases in these countries [5]. In the current study, the number of children and adolescents with high myopia is comparatively low (0.06 %, n = 12 for SE ≤ -5.0 D and 0.02 %, n = 3 for SE ≤ -6.0 D, see also Fig 1 and 2).

Hyperopia

In our study, hyperopia was found in 9.4 % of the studied population. Earlier, a prevalence rate of 5.8 % was reported for children and adolescents in Germany, based on parent-reported questionnaires [16]. Due to accommodation hyperopic children often do not experience a reduction of visual quality and therefore might not consult the ophthalmologist. For this reason, hyperopic refractive errors often remain undiagnosed. Therefore, analyzing data only on children wearing spectacles is a significant limitation of studies like Jobke and colleagues [16]. The current results are similar to findings of hyperopia prevalence rates of 7.7 % and 9.1 % in the Netherlands [33] and Sweden [34]. Higher prevalence rates were observed in Australian children aged 4 to 12 years (38.4 %) [35]. Furthermore, our results demonstrate a lower prevalence of hyperopia in older children, which is in line with the process of emmetropization. A gender difference was not observed. These findings are also supported by other European studies [16,36].

Anisometropia

In the current study, 3.7 % of all children and adolescents had an anisometropia (≥ 1.0 D). This finding is comparable with findings on Swedish [34] (2.8 %) and Dutch children [33] (4.6 %). However, Junghans et al. [37] found an anisometropia prevalence of only 1.4 % in Australian children.

Astigmatism

The astigmatism prevalence of 11.8 % observed in the present study was lower than previously found in Chinese schoolchildren aged 4 to 16 years (36 %) [10]. However, higher lid tension in Asian people is suggested to be associated with a higher prevalence of astigmatism [38]. Australian schoolchildren showed similar prevalence rates of 8.3 % for children aged 5 to 10 years and 10.5 % in 11- to 20-year-old children [39], compared to our study.

Strengths & limitations

The present paper presents, for the first time in Germany, measurement-based data describing the refractive status in children and adolescents. Other strengths were the large age range with a high participation rate of children in all age-groups**.** The limitation of our study was that cycloplegia was not performed due to ethical and organizational reasons. As stated previously, accommodation might affect the refractive error leading to an overestimation of myopia or an underestimation of hyperopia. In addition, hyperopia might be undetected. Finally, the generalizability of study findings to the whole population of German children might be limited due to a slight underrepresentation of children from lower social strata and from rural areas in the LIFE Child study sample.

Conclusions

The prevalence of myopia in German children and adolescents increases with child age. The overall myopia prevalence in children in Germany aged 3 to 16 years is around or even less than 10%, taking into consideration that measurements were carried out without cycloplegica. Our results are comparable to other European paediatric studies. Even though the mean prevalence of myopia (10,8 %) is (still) lower than in other, East Asian countries, it is a health concern that should be taken seriously, for example because of the risk of myopia-related secondary diseases in adulthood. The risk for these diseases, such as myopic maculopathy and retinal detachment, increases with increasing level of myopia. Measures to reduce myopia (e.g. by limiting near-work activity and promoting outdoor activity) should start in early childhood and be followed up consistently.

Acknowledgements

We wish to thank all of the children and parents who have participated in the LIFE Child study and all the research assistants in the LIFE Child team. We acknowledge support from Leipzig University for Open Access Publishing.

References

1. Flaxman SR, Bourne, Rupert R A, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5(12):1221–1234. doi:10.1016/S2214-109X(17)30393-5

2. Mitchell P, Hourihan F, Sandbach J, Jin Wang J. The relationship between glaucoma and myopia. *Ophthalmology*. 1999;106(10):2010-2015. doi:10.1016/S0161-6420(99)90416-5

3. Bullimore MA, Brennan NA. Myopia control: Why each diopter matters. *Optom Vis Sci*. 2019;96(6):463-465. doi:10.1097/OPX.0000000000001367

4. Lim R, Mitchell P, Cumming R. Refractive associations with cataract: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci*. 1999;106(10):2010-2015.

5. Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res*. 2012;31(6):622-660. doi:10.1016/j.preteyeres.2012.06.004

6. Kulp MT, Ying G-S, Huang J, et al. Associations between hyperopia and other vision and refractive error characteristics. *Optom Vis Sci*. 2014;91(4):383-389. doi:10.1097/OPX.0000000000000223.

7. Naidoo KS, Fricke TR, Frick KD, et al. Potential lost productivity resulting from the global burden of myopia: Systematic review, meta-analysis, and modeling. *Ophthalmology*. 2019;126(3):338-346. doi:10.1016/j.ophtha.2018.10.029

8. Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123(5):1036-1042. doi:10.1016/j.ophtha.2016.01.006

9. Hashemi H, Yekta A, Nabovati P, Khoshhal F, Riazi A, Khabazkhoob M. The prevalence of refractive errors in 5-15 year-old population of two underserved rural areas of Iran. *J Curr Ophthalmol*. 2018;30(3):250-254. doi:10.1016/j.joco.2017.05.004

10. Wu JF, Bi HS, Wang SM, et al. Refractive error, visual acuity and causes of vision loss in children in Shandong, China. The Shandong Children Eye Study. *PloS One*. 2013;8(12):82763. doi:10.1371/journal.pone.0082763

11. Czepita D, Zejmo M, Mojsa A. Prevalence of myopia and hyperopia in a population of Polish schoolchildren. *Ophthalmic Physiol Opt*. 2007;27(1):60-65. doi:10.1111/j.1475-1313.2006.00419.x

12. Villarreal MG, Ohlsson J, Abrahamsson M, Sjöström A, Sjöstrand J. Myopisation: The refractive tendency in teenagers. Prevalence of myopia among young teenagers in Sweden. *Acta Ophthalmol Scand*. 2000;(78):177-181.

13. McCullough SJ, O'Donoghue L, Saunders KJ. Six year refractive change among white children and young adults: Evidence for significant increase in myopia among white UK children. *PLOS ONE*. 2016;11(1):e0146332. doi:10.1371/journal.pone.0146332

14. Käsmann-Kellner B, Heine M, Pfau B, Singer A, Ruprecht KW. Screening-Untersuchung auf Amblyopie, Strabismus und Refraktionsanomalie bei 1030 Kindergartenkindern. *Klin Monbl Augenheilkd*. 1998;213:166-173.

15. Schuster AK, Elflein HM, Pokora R, Urschitz MS. Prävalenz und Risikofaktoren der Kurzsichtigkeit bei Kindern und Jugendlichen in Deutschland – Ergebnisse der KiGGS-Studie. *Klin Padiatr*. 2017;229(4):234-240. doi:10.1055/s-0043-102938

16. Jobke S, Kasten E, Vorwerk C. The prevalence rates of refractive errors among children, adolescents, and adults in Germany. *Clin Ophthalmol*. 2008;2(3):601-607.

17. Poulain T, Baber R, Vogel M, et al. The LIFE Child study: a population-based perinatal and pediatric cohort in Germany. *Eur J Epidemiol*. 2017;32(2):145-158. doi:10.1007/s10654-016-0216-9

18. Quante M, Hesse M, Döhnert M, et al. The LIFE child study: a life course approach to disease and health. *BMC Public Health*. 2012;12:1021. doi:10.1186/1471-2458-12-1021

19. Lin Z, Vasudevan B, Ciuffreda KJ, et al. The difference between cycloplegic and non-cycloplegic autorefraction and its association with progression of refractive error in Beijing urban children. *Ophthalmic Physiol Opt*. 2017;37(4):489-497. doi:10.1111/opo.12381

20. Hashemi H, Fotouhi A, Yekta A, Pakzad R, Ostadimoghaddam H, Khabazkhoob M. Global and regional estimates of prevalence of refractive errors: Systematic review and meta-analysis. *J Curr Ophthalmol*. 2018;30(1):3-22. doi:10.1016/j.joco.2017.08.009

21. Flitcroft DI, He M, Jonas JB, et al. IMI – Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiologic Studies. *Invest Ophthalmol Vis Sci*. 2019;60(3):M20-M30. doi:10.1167/iovs.18-25957

22. Deng L, Gwiazda JE. Anisometropia in children from infancy to 15 years. *Invest Ophthalmol Vis Sci*. 2012;53(7):3782-3787. doi:10.1167/iovs.11-8727

23. Lampert T, Müters S, Stolzenberg H, Kroll LE. [Measurement of socioeconomic status in the KiGGS study. First follow-up (KiGGS Wave 1)]. *Bundesgesundheitsblatt*. 2014;57:762-770.

24. Rauscher FG, Lange H, Yahiaoui-Doktor M, et al. Agreement and repeatability of noncycloplegic and cycloplegic wavefront-based autorefraction in children. *Optom Vis Sci*. 2019;96(11):879-889. doi:10.1097/OPX.0000000000001444

25. Sankaridurg P, He X, Naduvilath T, et al. Comparison of noncycloplegic and cycloplegic autorefraction in categorizing refractive error data in children. *Acta Ophthalmol (Copenh)*. 2017;95(7):633-640. doi:10.1111/aos.13569

26. You QS, Wu LJ, Duan JL, et al. Prevalence of myopia in school children in greater Beijing: the Beijing Childhood Eye Study. *Acta Ophthalmol (Copenh)*. 2014;92(5):398–406. doi:10.1111/aos.12299

27. Morgan IG, Ohno-Matsui K, Saw S-M. Myopia. *The Lancet*. 2012;379(9827):1739-1748.

28. Rudnicka AR, Kapetanakis VV, Wathern AK, et al. Global variations and time trends in the prevalence of childhood myopia, a systematic review and quantitative meta-analysis:

implications for aetiology and early prevention. *Br J Ophthalmol*. 2016;100(7):882-890. doi:10.1136/bjophthalmol-2015-307724

29. Popović-Beganović A, Zvorničanin J, Vrbljanac V, Zvorničanin E. The prevalence of refractive errors and visual impairment among school children in Brčko district, Bosnia and Herzegovina. *Semin Ophthalmol*. 2018;33(7-8):858-868.

30. Lam CS-Y, Lam C-H, Cheng SC-K, Chan LY-L. Prevalence of myopia among Hong Kong Chinese schoolchildren: changes over two decades. *Ophthalmic Physiol Opt*. 2012;32(1):17-24. doi:10.1111/j.1475-1313.2011.00886.x

31. Lu B, Congdon N, Liu X. Associations between near work, outdoor activity, and myopia among adolescent students in rural China: The Xichang Pediatric Refractive Error Study Report No. 2. *Arch Ophthalmol*. 2009;127(6):769-775.

32. Flitcroft DI. Emmetropisation and the aetiology of refractive errors. *Eye*. 2014;28(2):169-179. doi:10.1038/eye.2013.276;

33. Hendricks TJW, de Brabander J, Vankan-Hendricks MH, van der Horst FG, Hendrikse F, Knottnerus JA. Prevalence of habitual refractive errors and anisometropia among Dutch schoolchildren and hospital employees. *Acta Ophthalmol (Copenh)*. 2009;87(5):538-543. doi:10.1111/j.1755-3768.2008.01251.x

34. Grönlund MA, Andersson S, Aring E, Hård A-L, Hellström A. Ophthalmological findings in a sample of Swedish children aged 4-15 years. *Acta Ophthalmol Scand*. 2006;84(2):169-176. doi:10.1111/j.1600-0420.2005.00615.x

35. Junghans B, Crewther S. Prevalence of myopia among primary school children in eastern Sydney. *Clin Exp Optom*. 2003;86(5):339-345.

36. O'Donoghue L, McClelland JF, Logan NS, Rudnicka AR, Owen CG, Saunders KJ. Refractive error and visual impairment in school children in Northern Ireland. *Br J Ophthalmol*. 2010;94(9):1155-1159. doi:10.1136/bjo.2009.176040

37. Junghans B, Kiely PM, Crewther DP, Crewther SG. Referral rates for a functional vision screening among a large cosmopolitan sample of Australian children. *Ophthalmic Physiol Opt*. 2002;(22):10-25.

38. Lam CS, Goh WS. Astigmatism among Chinese school children. *Clin Exp Optom*. 1991;(74):146-150.

39. Sanfilippo PG, Yazar S, Kearns L, Sherwin JC, Hewitt AW, Mackey DA. Distribution of astigmatism as a function of age in an Australian population. *Acta Ophthalmol (Copenh)*. 2015;93(5):377-385. doi:10.1111/aos.12644

PLOS ONE

RESEARCH ARTICLE

Reference curves for refraction in a German cohort of healthy children and adolescents

Carolin Truckenbrod[1]*, Christof Meigen[1,2], Manuela Brandt[1], Mandy Vogel[1,2], Siegfried Wahl[3,4], Anne Jurkutat[1], Wieland Kiess[1,2,5]

1 LIFE Leipzig Research Center for Civilization Diseases, University of Leipzig, Leipzig, Germany, **2** Department of Women and Child Health, University Hospital for Children and Adolescents and Center for Pediatric Research, Leipzig University, Leipzig, Germany, **3** Institute for Ophthalmic Research, Eberhard Karls University Tuebingen, Tuebingen, Germany, **4** Carl Zeiss Vision International GmbH, Aalen, Germany, **5** Center for Pediatric Research, Leipzig University, Leipzig, Germany

* carolin.truckenbrod@t-online.de

Citation: Truckenbrod C, Meigen C, Brandt M, Vogel M, Wahl S, Jurkutat A, et al. (2020) Reference curves for refraction in a German cohort of healthy children and adolescents. PLoS ONE 15 (3): e0230291. https://doi.org/10.1371/journal.pone.0230291

Editor: Hidenaga Kobashi, Keio University School of Medicine, JAPAN

Received: December 10, 2019

Accepted: February 25, 2020

Published: March 11, 2020

Data Availability Statement: There exist ethical restrictions on sharing pseudonymized data sets. The LIFE Child study is a study collecting potentially sensitive information. Publishing data sets is not covered by the informed consent provided by the study participants. Furthermore, the data protection concept of LIFE requests that all (external as well as internal) researchers interested in accessing data sign a project agreement. Researchers that are interested in accessing and analyzing data collected in the LIFE Child study

Abstract

Purpose

Percentile curves of refractive development for German children were generated. We hypothesize that refraction in children in central Europe might differ from data in central Asia.

Methods

Non-cycloplegic refraction was measured using the ZEISS i.Profiler plus (Carl Zeiss Vision GmbH, Germany) in 1999 children, of which were 1046 male and 953 female, aged 3 to 18 years. Reference curves were calculated with the R-package GAMLSS as continuous function of age.

Results

There were only little differences for all centiles between the genders at 3 years and a general trend towards more myopia with increasing age. For the 97th centile and the 3rd centile, girls showed higher myopia/ less hyperopia than boys. Between the age of 3 and 18, the median refraction became -0.68 D and -0.74 D more myopic for boys and girls, respectively. At the same time, the 97th centile for boys changed +0.29 D towards hyperopia and in girls -0.52 D towards myopia. A general myopic trend was seen in the 3rd centile, which was -2.46 D for boys and -2.98 D for girls. For both genders, the median became less than zero at the age of 10 years but did not become myopic (less than -0.5 D) up to the age of 18.

Conclusion

Our analysis presents the first reference curve for refraction in central Europe. In comparison to data from China and Korea, there is only little difference at the age of 5 years in all centiles which then increases continuously. For all ethnicities, a trend towards myopia with increasing age could be observed, but myopia progression is much higher in China and Korea than in Germany. The most marked differences can be seen in the lower centiles.

may contact the data use and access committee (dm@life.uni-leipzig.de).

Funding: Funding was received from Carl Zeiss International GmbH. The funder provided support in the form of salaries for author SW, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the 'author contributions' section.

Competing interests: This work was supported by Carl Zeiss Vision International GmbH. S. Wahl is employed by Carl Zeiss Vision International GmbH. LIFE Child uses the Zeiss i.Profiler on free loan from Carl Zeiss Vision International GmbH for the purpose of the studies. This does not alter our adherence to all the PLOS ONE policies on sharing data and materials, as detailed online in the guide for authors.

Further investigations should clarify whether commencement of preschool activities with prolonged near-work initiates the divergence in refractive development.

Introduction

Reference centile curves are commonly used in paediatric practice in order to estimate body height and weight development. They are used as a screening tool to assess the development and well-being of children [1,2].

Chen et al. have introduced the use of reference curves for refractive development in order to identify children at risk for high myopia [3]. Once children at risk to develop high myopia are identified, a treatment to slow down myopia progression can be commenced, like the use of atropine eyedrops, Orthokeratology or contact lenses for myopia treatment [4]. The use of centile curves to predict future refractive development is conclusive, as Zadnik et al. have shown that the current refraction in children is the most important predictive factor for myopia onset [5].

However, centile curves for refraction are population-specific [6,7]. Therefore Chen et al., whose study was carried out in Guangzhou, China, have called for more studies to generate centile curves for refraction [3]. Incidence, progression and prevalence of myopia differs tremendously from Asia to Europe. The prevalence of myopia for children between 5 and 16 years in Hong Kong is 36.7% with a progression from 18.3% at 6 years of age to 61.5% at 12 years of age [8]. In Germany, the prevalence of myopia is 13.3% for the age group 3 to 17 years. The progression of myopia in the age groups 3 to 6 and 11 to 13 was 2.4% to 13.6% and 2.1% to 19.3% for boys and girls, respectively [9]. The trend towards high myopia is much smaller in paediatric cohorts in Germany, compared to Asia [7]. Between 2000 and 2015 the prevalence of myopia did not increase in Germany [10]. High myopia in the adult age is associated with higher risks for complications, such as myopic maculopathy [11] and retinal detachment [12]. But not only children with risk for high myopia can be treated with atropine, orthokeratology or special contact lenses. These options are open to all myopic children [11], although a smaller amount of myopia is associated with a smaller risk for complications [11]. Therefore the use of centile curves is interesting for any population.

Centile curves allow also for comparison of refractive development of different populations. Instead of comparing only the refractive state of the population at a certain age, trends can be compared with reference curves. Finding the age at which refractive development starts to differ between ethnicities may help to find the cause for the difference in myopia prevalence between Asia and Europe. Whereas the differences of myopia among populations are studied thoroughly, there are fewer data about the differences of hyperopia development [13–15]. This gap can be closed by comparison of centile curves.

Hyperopia can be classified in mild hyperopia (>0.5 D to ≤ +2.0 D), moderate hyperopia (>+2.0 D to ≤ +5.0 D) and high hyperopia (>+ 5.0 D) [16]. In Shandong in China, the prevalence of mild hyperopia decreases continuously from 77.4% at the age of 4 years to 7.5% at 18 years and the prevalence of moderate and high hyperopia diminishes from 14.8% at 4 years to 1.4% at 12 years and is relatively stable thereafter [14]. There is a general trend towards regression of hyperopia in China with higher regression rates in children with high hyperopia compared to children with moderate hyperopia [15]. In Germany, the prevalence of all hyperopics >+0.5 D, measured without cycloplegia, decreased from 17.2% at the age of 3 to 4.5% at the age of 11 and is relatively stable thereafter [17].

Materials and methods

Study design

This analysis is part of the LIFE Child study, which was established to monitor healthy child development. It consists of three cohorts, which are interrelated: the birth cohort, health cohort and obesity cohort. LIFE Child is, among others, one of the biggest ongoing longitudinal and cross sectional studies in Europe, to understand a wide range of factors influencing health and growth in children [18]. It takes place in Leipzig, Germany and aims to indicate representative data [18]. Despite many efforts, the study population shows a bias towards a higher educational and socioeconomic status [18,19]. Designed as a longitudinal and cross sectional study, participants are invited once a year for continuous measurements. At each visit, a consent form is to be signed by a parent, by the child if possible and a physician or physician assistant. The study was approved by the Ethical Committee of the medical faculty of the University of Leipzig (Reg. No. 264-10-ek) and registered with the trail number NCT02550236.

Data from 1999 participants of 1411 families from the health and obesity cohort between the age of 3 and 18 years, of which were 1046 boys and 953 girls, were analysed. The data was collected between January 2014 and May 2018.

Measurements

Autorefraction without cycloplegia was carried out with the wavefront aberrometer ZEISS i.Profiler plus (Carl Zeiss Vision GmbH, Germany), which is based on a Hartmann-Shack sensor. The refractive error was analysed at a 3mm pupil and a vertex distance of 12mm. In our study setting, it was not possible to apply cycloplegica, as the ethical commission denied the use of cycloplegia. For conducting the measurements, the light was switched off and the window blinds were closed. Only the light emitted by the computer screens illuminated the room. Three measurements of each eye were carried out for each patient, whereby the individual eyes were measured in an alternating manner. If the children were not able to concentrate over the whole study period, the measurements were discontinued after one or two trials.

In order to relax accommodation, the focus target is defocused initially (fogging). Before the aberrometry commences this defocus is reduced and the participant can see the target clearly.

After autorefraction the uncorrected visual acuity (UCVA) and the best corrected visual acuity (BCVA) were obtained using the ZEISS i.Polatest® (Carl Zeiss Vision GmbH, Aalen, Germany) with the spherocylindrical combination measured with the ZEISS i.Profiler plus. For children from 3 to 6 years and older children who were not able to read, Colt Symbols were used, for the older children letters. The test distance was 6 meters with mirror.

Statistical analysis

According to the WHO guidelines for attained growth curves, the refraction is presented as a continous function of age. This results in smoother curves than using age intervals and provides better comparableness. The GAMLSS model allows for creating such reference curves from continuous variables [1,2]. For statistical analysis, the software R, by the R foundation, with the additional package "gamlss" was used. This method has been used in former papers analysing the LIFE Child database in order to create reference curves [20,21]. While the LMS distribution is the most commonly used with this method [2] it does not allow modelling of negative values, which are present in the spherical equivalent. We, therefore, used the slightly more flexible skew exponential power type 2 distribution (SEP2) of the same package. For comparison with (Cheng), 3rd, 50^{th}, and 97^{th} percentiles were calculated, but other values could be easily obtained from the fitted models [22].

Data collected was longitudinal with the first visit at different ages. Especially for the older age groups, sufficient data is only available when data from follow-up visits are taken into account. Furthermore, some of the study population are siblings and data therefore interrelated. As this problem exists for all statistical analyses within the LIFE Child study a method has been developed to generate reference intervals from unbalanced, interrelated data [23].

Of all three measurements, the spherical equivalent (SE) of the right eye was calculated (SE = sphere + ½ cylinder). The median out of the three measurements was used for reference interval calculation. If only two measurements were obtained, the more positive one was chosen for calculation. We used this procedure, as the non-cycloplegic measurement is commonly lower than the corresponding cycloplegic measurement [24], so the more positive (or less negative) result would be closer to a cycloplegic result. In case only one measurement was taken this was used for calculation. Less than three measurements appeared mainly in young children, but already 87.4% of 3-year-olds had all three measurements taken, compared to 100% of 17 year olds. In order to evaluate as many data of different children as possible, we decided not to discard the results with less than three measurements.

Results

Using the GAMLSS package of the R software reference intervals were created for the refraction development over age of the right eye for boys and girls separately. Fig 1 shows the 3^{rd}, 50^{th} and 97^{th} centile curve of refractive development and Table 1 shows the differences of refractive development between boys and girls. The reference intervals cover the age interval from 3 up to 18 years. The non-cycloplegic spherical equivalent, obtained by wavefront-based autorefraction is shown. We followed the most common definition of myopia for non-cycloplegic measurements and defined myopia as SE $<$ -0.5 D (7). In the graph, the myopia cut-off is shown as dashed line.

The 50^{th} centile does not differ between boys and girls and shows a general trend towards a myopic shift. At 3 years of age, the median refraction is 0.37 D for boys and 0.31 D for girls. At 18 years, the median has shifted to -0.31 D in boys and -0.43 in girls. Thus the myopic shift of the median between the age of 3 and 18 years is -0.68 D and -0.74 D for boys and girls, respectively. For both genders, the median becomes less than zero at the age of 10 years but does not become myopic (less than -0.5 D) up to the age of 18.

At 3 years of age, data does not show differences between the genders. The 97^{th} centile is 1.92 D for boys and 2.0 D for girls and the 3^{rd} centile is -0.93 for boys and -0.96 for girls. While in the hyperopic boys of the 97^{th} centile there is a subtle hyperopic shift to 2.21 D (+ 0.29 D between the age of 3 and 18), girls show the opposite trend to 1.48 D (-0.52 D in the observed period).

During the whole observation period, the gap between the 3^{rd} centile between boys and girls increases. The 3^{rd} centile cut-off is -3.39 D for boys and -3.94 for girls at the age of 18. Both genders show a myopic shift in the 3^{rd} centile, which was -2.46 for boys and -2.98 for girls.

It can be seen that the upper centiles show in general less changes throughout age groups compared to the lower centiles. With increasing age, the myopic shift of the 3^{rd} centile is faster up to the end of the observed period.

In general, there is a trend to more myopic development in girls, compared to boys.

In order to compare refraction reference curves between Germany and China we had to transfer our data from non-cycloplegic measurements into adequate cycloplegic measurement results. Figs 2 and 3 and Table 2 show reference curves for boys and girls in the RESC study in China [3] in comparison to data from the LIFE Child study in Germany.

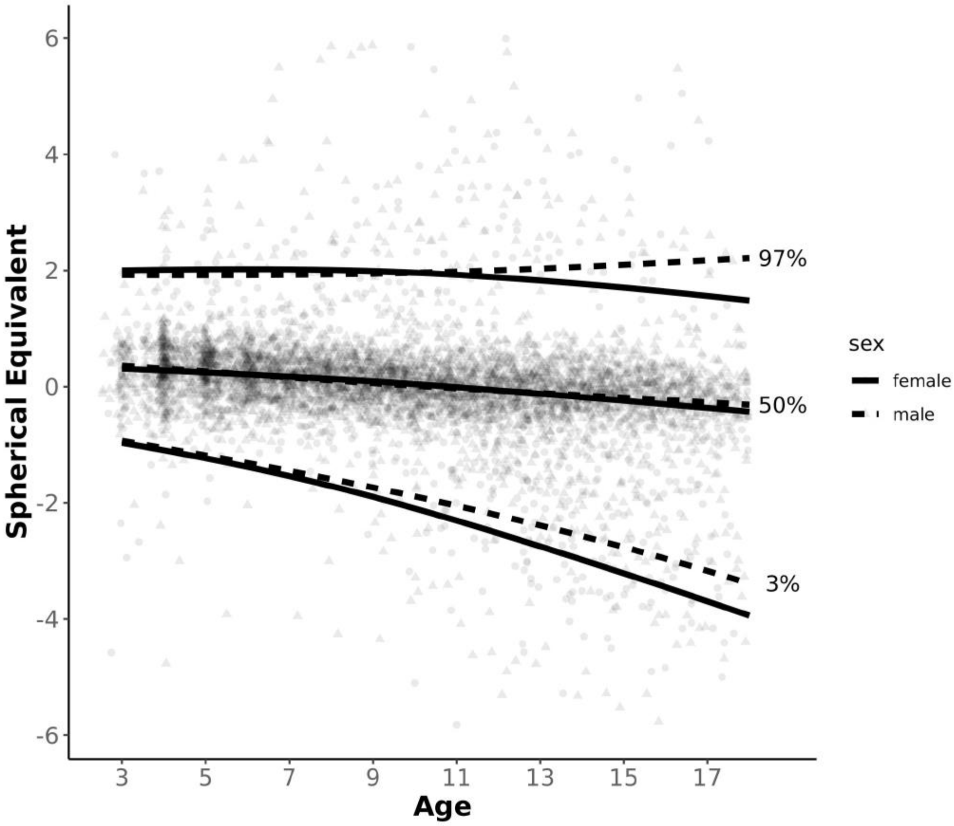

Fig 1. Reference curves for non-cycloplegic autorefraction (spherical equivalent) over age. Analysed were 953 girls and 1046 boys of the LIFE Child study population. The lines show the 3rd, 50th and 97th centile. Each dot represents a single measurement.

https://doi.org/10.1371/journal.pone.0230291.g001

In the RESC study data was only collected from the age of 5 to 15. Therefore we can only compare refraction curves of this age group. While our data does not show differences between boys and girls in the 50th centile over all age groups, the 50th centile of boys and girls in China developed similarly up to the age of 10 years. Above the age of 10, there was an increasing gap between the myopic shift between the genders in China. At 15 years, girls in the 50th centile were 0.89 D more myopic than boys, which is clinically relevant. In the 3rd centile girls in Germany became increasingly more myopic than boys. This trend could be seen in China as well, but only up to the age of 10 years. The trend reversed, and at 15 years, boys in the RESC study were more myopic than girls.

Comparing the adjusted data for non-cycloplegic measurements, mean refraction at the age of 5 was 1.39 D in Germany and 0.92 D in China for boys and 1.46 D for German girls compared to 1.00 D for Chinese girls. The mean refraction for both genders is almost half a dioptre

Table 1. 3rd, 50th and 97th centile cut-offs in diopters for boys and girls and comparison between the genders of the LIFE study population.

Age	Boys [D]				Girls [D]				Difference (girls-boys) [D]		
	N*	C3	C50	C97	N*	C3	C50	C97	C3	C50	C97
3	61	-0.93	0.37	1.92	60	-0.96	0.31	2.00	-0.03	-0.06	0.08
4	183	-1.06	0.31	1.92	149	-1.09	0.28	2.01	-0.04	-0.04	0.09
5	170	-1.18	0.26	1.92	164	-1.23	0.24	2.02	-0.05	-0.02	0.10
6	159	-1.31	0.21	1.92	166	-1.38	0.21	2.02	-0.07	0.00	0.10
7	158	-1.45	0.16	1.93	167	-1.54	0.17	2.02	-0.09	0.01	0.09
8	172	-1.59	0.11	1.94	161	-1.71	0.13	2.01	-0.12	0.02	0.07
9	200	-1.74	0.06	1.95	151	-1.90	0.09	1.99	-0.16	0.03	0.04
10	190	-1.89	0.02	1.96	145	-2.10	0.04	1.96	-0.21	0.03	0.00
11	184	-2.05	-0.03	1.98	137	-2.31	-0.01	1.93	-0.26	0.02	-0.05
12	186	-2.21	-0.07	2.00	162	-2.52	-0.06	1.88	-0.31	0.01	-0.12
13	166	-2.39	-0.11	2.03	167	-2.75	-0.12	1.83	-0.36	-0.01	-0.21
14	160	-2.57	-0.15	2.07	163	-2.98	-0.18	1.77	-0.41	-0.03	-0.30
15	136	-2.76	-0.19	2.10	126	-3.21	-0.24	1.71	-0.45	-0.05	-0.39
16	119	-2.96	-0.23	2.14	116	-3.45	-0.30	1.64	-0.49	-0.07	-0.50
17	90	-3.17	-0.27	2.18	85	-3.69	-0.37	1.56	-0.52	-0.10	-0.61
18	35	-3.39	-0.31	2.21	27	-3.94	-0.43	1.48	-0.55	-0.12	-0.73

N* states the number of participants in each age group. One participant can be present in several age groups, but in the statistical analysis each participant is weighted equally regardless of the number of visits.

https://doi.org/10.1371/journal.pone.0230291.t001

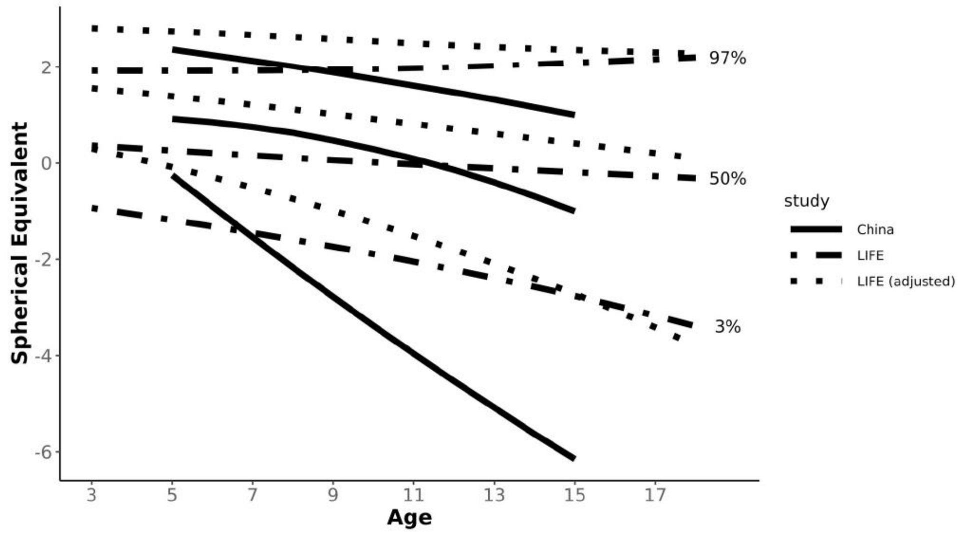

Fig 2. 3rd, 50th, 97th centile reference curves of refraction over age for boys. The dashed lines represent the data of the LIFE Child study, the dotted lines the transferred data of LIFE Child study by the calculation of Sakaridurg et al. into comparable data for cycloplegia and the continous lines show the results of the RESC study from a city in China [3].

https://doi.org/10.1371/journal.pone.0230291.g002

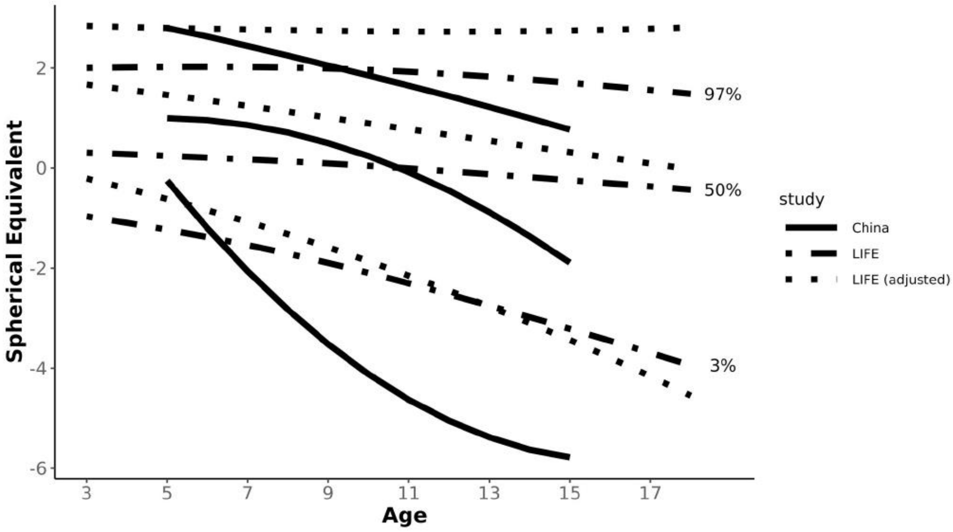

Fig 3. 3rd, 50th, 97th centile reference curves of refraction over age for girls. The dashed lines represent the data of the LIFE Child study, the dotted lines the transferred data of LIFE Child study by the calculation of Sakaridurg et al. into comparable data for cycloplegia and the continous lines show the results of the RESC study from a city in China [3].

https://doi.org/10.1371/journal.pone.0230291.g003

more myopic in China at the age of 5 years. This difference increases up to the age of 15 to 1.41 D in boys and 2.21 D in girls, showing a stronger trend towards myopia in China.

At age 5 there is little difference between both ethnicities for the 3rd centile. Boys in China are slightly more myopic (0.17D) and Chinese girls are even 0.37 D less myopic than German girls. Already in 6 year old children differences begin to increase with Chinese children becoming more myopic than German children. At the age of 15, the gap is 3.43 D for boys and 2.34 D for girls.

Table 2. Differences of 3rd, 50th and 97th centile cutoffs in diopters for boys and girls between LIFE child data (adjusted by the calculation of Sankaridurg et al) and RECS study.

Age	Boys (Adjusted LIFE Data—RECS study) [D]			Girls (Adjusted LIFE Data—RECS study) [D]		
	C3	C50	C97	C3	C50	C97
5	0.17	0.47	0.38	-0.37	0.46	0.00
6	0.61	0.45	0.46	0.36	0.39	0.16
7	1.03	0.46	0.54	0.99	0.38	0.33
8	1.43	0.48	0.62	1.51	0.42	0.51
9	1.79	0.55	0.70	1.94	0.51	0.70
10	2.14	0.63	0.80	2.26	0.65	0.88
11	2.45	0.72	0.90	2.48	0.86	1.08
12	2.73	0.85	1.00	2.60	1.11	1.29
13	2.99	1.01	1.11	2.61	1.43	1.51
14	3.23	1.20	1.24	2.53	1.79	1.74
15	3.43	1.41	1.37	2.34	2.21	1.98

https://doi.org/10.1371/journal.pone.0230291.t002

For the 97th centile, however, data at age 5 shows no differences for girls and boys are 0.38 D less hyperopic in China. For 15 year old children, the differences between the ethnicities are similar to the differences of the 50th centile.

While at age 5 there is in general little difference, the Chinese population shows for all centiles a more myopic/ less hyperopic development up to the age of 15.

Discussion

Because our data was measured without cycloplegia but Chen et al. measured refraction under cycloplegia, the data cannot be compared directly.

Sankaridurg et al. have tried to tackle this problem and proposed a calculation which allows prediction of cycloplegic refraction from non-cycloplegic refraction. In their setting, they analysed data of 4 to 15 year old children in Shanghai with and without cycloplegia. Autorefraction was carried out with the Topcon K R-8900, which is not wavefront-based. They found that the difference between non-cycloplegic and cycloplegic autorefraction was -0.63 D on average. The difference was dependent on age, refraction and visual acuity. The deviation between cycloplegic and non-cycloplegic measurements would be highest for young hyperopic children and lowest for older myopic children [25]. Accommodation is generally higher in younger children [25] and, naturally, more hyperopic children are used to accommodate even more.

For 13 year old children, Sanfilippo et al. found similar differences from non-cycloplegic to cycloplegic autorefraction with the Humphrey-598 automated refractor in Australia, suggesting that this relation can be adopted to other ethnicities [26]. Other studies in Australia using the Canon-RK-F1 autorefractor and in China with the Nikon Retinomax K-Plus autorefractor found even higher differences between cycloplegic and non-cycloplegic autorefraction [24,27].

One might argue that the calculation by Sankaridurg et al. is based on autorefraction, but not wavefront-based autorefraction. However, it has been shown that there is no difference between the two methods of obtaining autorefraction. For adults the results taken by the i.Profiler Plus (Carl Zeiss Vision, Aalen) are comparable to the results by the Canon RK 2F autorefractor [28]. The same relation has been shown for other autorefractors and Hartmann-Shak sensors [29].

Using the formula of the "model B" from Sankaridurg et al. [25] we aim to convert our set of data into the equivalent of cycloplegic data in order to be able to compare centile curves. Both Sankaridurg et al. and Chen et al. used 1% cyclopentolate instilled 5 minutes apart for cycloplegia. As both used the same cycloplegic drug and the same procedure we could compare our transferred results to the results of the RESC study. Figs 2 and 3 show the 3rd, 50th e and 97th centile for boys and girls of the RESC study (solid lines) and LIFE Child study original dataset and the transformed data to cycloplegia (dashed and dotted lines, respectively).

Through this transformation our data became more positive in general. The difference between non-cycloplegic and cycloplegic refraction decreased with age. The calculated cycloplegic comparative value was dependent on age, refraction and uncorrected visual acuity. On average, the difference between the LIFE Child measured data and the calculated values was -0.75 D. That means, that the corresponding cycloplegic data should be +0.75 D more hyperopic on average.

Chen et al. were the first study group (RESC study) to publish centile curves for refraction development in children and adolescents. Data for their study was collected in Guangzhou city in China [3]. The prevalence of myopia is much higher in Asia compared to Europe [7]. We seek to discuss the differences in percentile curves between China and Germany. Our aim is to find the point of time when overall development of refraction diverges, as the prevalence of myopia and the prevalence of pathologic myopia below -6.0 D are much higher in Asia [7].

Our study population shows overall a more hyperopic and less myopic structure. This difference increases with age. At the end of the observed age period. the 50th and 97th centile differences between the girls are more pronounced than differences in boys. For both genders, the largest differences can be seen in the 3rd centile, which are more distinct in boys than in girls. For myopic children the difference is much higher than for the rest of the study population. While the higher prevalence of myopia and especially high myopia explains the huge deviation of the 3rd centile at age 15 between both ethnicities, it is interesting that there is also a marked deviation of the 97th centile. The prevalence of hyperopia of more than 2 Diopters in China in 5 year old children is 17.0% and in 15 year old children below 1% [30]. Data for Europe measured in a comparable manner was only available for the age group 25 to 29. The prevalence of hyperopia of at least one Diopter was 6.4% and high hyperopia with at least 3 Diopters 1.1% [31]. Assuming that the prevalence of hyperopia does not increase in early adulthood, the prevalence of hyperopia is very likely higher in Europe compared to Germany. While the 97th centile for the adjusted German data is within the range of hyperopia for all age groups, in the 97th centile of the Chinese population it is clearly visible that less than 3% of the Children at age 15 are hyperopic with more than 2 Diopters. As there was no 99.5th centile given from the RECS study we were not able to compare the development of refraction of these children who are likely to stay hyperopic in both ethnicities.

The deviation of the 3rd centile may be due to differences in the school system. At 5 years of age, Chinese children start pre-primary school. At 6 years, both children in Germany and China start primary school. Where there are only 5 school-days per week in Germany with lesson times from around 8:00 am to 12:00 am for the first school years and only little homework, in china school times are from around 7:30 am to 4:00 pm with more homework and less holidays [32]. As postulated before [6–8,33], this suggests that more near-work and less time spent outside is one of the reasons for the prevalence of myopia rocketing in China. But it is likely, that there is also a genetic component, as there are already differences at the age of 5 before school starts in either of the countries.

Kim and Lim have also published centile curves of a large population of the KNHANES IV-V study in Korea aged 5 to 20 years [34]. Their data was measured with the KR-8800 Topcon Autorefractor without cycloplegia. However, data in this study was not analysed separately between boys and girls. Data are only given for the 10th and the 90th centile. At 5 years the 90th centile was +0.72 D in Korea, +1.11 D for German girls and +1.07 D for German boys. The 50th centile was 0.04 D in Korea, 0.24 D in German girls and 0.26 D in German boys and the 10th centile -0.75 D for Korea and -0.45 D and -0.42 D for German girls and boys, respectively. Compared to data of the LIFE Child study values for boys at 5 years do not differ much between the ethnicities with a general tendency of a more myopic structure in Korea. At 20 years however, the 90th centile in Korea is -0.25 D, the 50th centile -2.88 D and the 10th centile -5.98 D. For German girls and boys, respectively the 90th centile is 0.44 D and 0.87 D, the 50th centile -0.43 D and -0.31 D and the 10th centile -2.19 D and -1.82 D for 18 year olds. The data for 18 years is not given in the paper by Kim and Lim. Therefore we can only compare data at age 18 from our setting to data at age 20 in Korea. However, there is over all a more myopic setting in Korea compared to the Life Child data at 18 years. The differences are very obvious and would also be marked, if children at exactly the same age were compared. The differences are higher for the lower centiles, which show the more myopic children.

Interestingly both, the RESC study and the KNHANES IV-V study showed only little differences in the 5 year old children compared to LIFE Child data. During the whole observation period, this difference increased, leading to a more myopic setting at the study end point in

China and Korea compared to Germany. For all populations, the progression rates towards myopia were higher for the more myopic children.

Limitations

When comparing the three individual results of non-cycloplegic autorefraction in our setting the repeatability was ±0.78 D. As the fluctuation between the individual measurements was higher than the yearly progression rate of myopia, it was not possible to analyse longitudinal data, which we collected in some of the patients over up to 4 years.

Without cycloplegia, accommodation cannot be controlled and despite the fogging process during the measurement there can be some accommodation leading to results which are more myopic or less hyperopic than a comparable measurement under cycloplegia [25,35].

However, for a screening or paediatric setting cycloplegia is not feasible. Therefore doctors should be aware of the overestimation of myopia and underestimation of hyperopia depending on age and refraction. Using autorefraction as screening tool only, not for diagnosis or correction with glasses, this method still gives a good evaluation of refractive status and general outliners.

Conclusion

For the first time, age-specific detailed refraction percentile curves of children and adolescents in Germany are presented. Compared to data from Asia there is only little difference until the age of 5 years. Thereafter, especially the difference in the 3rd percentiles between the LIFE Child data and the data from Guangzhou increases dramatically. While there is only little alteration in the 97th centile in Germany, the trend towards less hyperopia or myopia can be seen in China also in the upper centile. However, for both populations the myopia progression rates increase with higher baseline myopia.

In order to predict future refractive development from the current refraction, longitudinal data needs to be collected and the predictive value of our percentile curves needs to be defined.

Acknowledgments

The authors are very grateful to all the families who have taken part in this study. The authors wish to thank the whole LIFE Child Team for their contributions to this work.

Author Contributions

Conceptualization: Carolin Truckenbrod, Christof Meigen.

Formal analysis: Christof Meigen, Mandy Vogel.

Funding acquisition: Wieland Kiess.

Investigation: Manuela Brandt.

Methodology: Carolin Truckenbrod.

Project administration: Wieland Kiess.

Resources: Siegfried Wahl.

Supervision: Wieland Kiess.

Validation: Christof Meigen.

Visualization: Christof Meigen.

Writing – original draft: Carolin Truckenbrod.

Writing – review & editing: Manuela Brandt, Mandy Vogel, Anne Jurkutat.

References

1. Borghi E, de Onis M, Garza C, van den Broeck J, Frongillo EA et al. (2006) Construction of the World Health Organization child growth standards: selection of methods for attained growth curves. Statistics in medicine 25 (2): 247–265. https://doi.org/10.1002/sim.2227 PMID: 16143968
2. Cole TJ, Green PJ (1992) Smoothing reference centile curves: The lms method and penalized likelihood. Statist. Med. 11 (10): 1305–1319.
3. Chen Y, Zhang J, Morgan IG, He M (2016) Identifying Children at Risk of High Myopia Using Population Centile Curves of Refraction. PloS one 11 (12): e0167642. https://doi.org/10.1371/journal.pone.0167642 PMID: 28030593
4. Cooper J, Tkatchenko AV (2018) A Review of Current Concepts of the Etiology and Treatment of Myopia. Eye & contact lens 44 (4): 231–247.
5. Zadnik K, Sinnott LT, Cotter SA, Jones-Jordan LA, Kleinstein RN et al. (2015) Prediction of Juvenile-Onset Myopia. JAMA ophthalmology 133 (6): 683–689. https://doi.org/10.1001/jamaophthalmol.2015.0471 PMID: 25837970
6. Wu P-C, Huang H-M, Yu H-J, Fang P-C, Chen C-T (2016) Epidemiology of Myopia. Asia-Pacific journal of ophthalmology (Philadelphia, Pa.) 5 (6): 386–393.
7. Foster PJ, Jiang Y (2014) Epidemiology of myopia. Eye (London, England) 28 (2): 202–208.
8. Fan DSP, Lam DSC, Lam RF, Lau JTF, Chong KS et al. (2004) Prevalence, incidence, and progression of myopia of school children in Hong Kong. Investigative ophthalmology & visual science 45 (4): 1071–1075.
9. Schuster AK, Elflein HM, Pokora R, Urschitz MS (2017) Prävalenz und Risikofaktoren der Kurzsichtigkeit bei Kindern und Jugendlichen in Deutschland—Ergebnisse der KiGGS-Studie. Klinische Padiatrie 229 (4): 234–240.
10. Wesemann W (2018) Analyse der Brillenstärken zeigt keine Zunahme der Myopie in Deutschland von 2000 bis 2015. Der Ophthalmologe: Zeitschrift der Deutschen Ophthalmologischen Gesellschaft 115 (5): 409–417.
11. Bullimore MA, Brennan NA (2019) Myopia Control: Why Each Diopter Matters. Optometry and vision science: official publication of the American Academy of Optometry 96 (6): 463–465.
12. Elnahry AG, Khafagy MM, Esmat SM, Mortada HA (2019) Prevalence and Associations of Posterior Segment Manifestations in a Cohort of Egyptian Patients with Pathological Myopia. Current eye research: 1–8.
13. Li T, Zhou X, Chen X, Qi H, Gao Q (2019) Refractive Error in Chinese Preschool Children: The Shanghai Study. Eye & contact lens 45 (3): 182–187.
14. Wu JF, Bi HS, Wang SM, Hu YY, Wu H et al. (2013) Refractive error, visual acuity and causes of vision loss in children in Shandong, China. The Shandong Children Eye Study. PloS one 8 (12): e82763. https://doi.org/10.1371/journal.pone.0082763 PMID: 24376575
15. Hu Y, Ding X, Zeng J, Cui D, Li C et al. (2019) Longitudinal Changes in Spherical Equivalent of Moderate to High Hyperopia: 2- to 8-Year Follow-Up of Children at an Initial Age of 5.5 to 8.4 Years. Investigative ophthalmology & visual science 60 (8): 3127–3134.
16. Moore BD, Augsburger AR, Ciner EB, Cockrell DA, Fern KD et al. (1997) Optometric clinical practice guideline: Care of the patient with hyperopia. Refrence Guide for Clinicians. St. Louis.
17. Brandt M, Meigen C, Vogel M, Poulain T, Jurkutat A et al. Refractive status in children and adolescents in a German pediatric cohort. Ophthalmic & physiological optics: the journal of the British College of Ophthalmic Opticians (Optometrists) 2019: submitted.
18. Quante M, Hesse M, Döhnert M, Fuchs M, Hirsch C et al. (2012) The LIFE child study: a life course approach to disease and health. BMC public health 12: 1021. https://doi.org/10.1186/1471-2458-12-1021 PMID: 23181778
19. Poulain T, Baber R, Vogel M, Pietzner D, Kirsten T et al. (2017) The LIFE Child study: a population-based perinatal and pediatric cohort in Germany. European journal of epidemiology 32 (2): 145–158. https://doi.org/10.1007/s10654-016-0216-9 PMID: 28144813
20. Bussler S, Vogel M, Pietzner D, Harms K, Buzek T et al. (2018) New pediatric percentiles of liver enzyme serum levels (alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase): Effects of age, sex, body mass index, and pubertal stage. Hepatology (Baltimore, Md.) 68 (4): 1319–1330.

21. Rieger K, Vogel M, Engel C, Ceglarek U, Thiery J et al. (2016) Reference intervals for iron-related blood parameters: results from a population-based cohort study (LIFE Child). LaboratoriumsMedizin 40 (1): 559.
22. Horowitz GL (2010) Defining, establishing, and verifying reference intervals in the clinical laboratory. Approved guideline. VIII, 61 S p.
23. Vogel M, Kirsten T, Kratzsch J, Engel C, Kiess W (2017) A combined approach to generate laboratory reference intervals using unbalanced longitudinal data. Journal of pediatric endocrinology & metabolism: JPEM 30 (7): 767–773.
24. Zhao J, Mao J, Luo R, Li F, Pokharel GP et al. (2004) Accuracy of noncycloplegic autorefraction in school-age children in China. Optometry and vision science: official publication of the American Academy of Optometry 81 (1): 49–55.
25. Sankaridurg P, He X, Naduvilath T, Lv M, Ho A et al. (2017) Comparison of noncycloplegic and cycloplegic autorefraction in categorizing refractive error data in children. Acta ophthalmologica 95 (7): e633–e640. https://doi.org/10.1111/aos.13569 PMID: 29110438
26. Sanfilippo PG, Chu B-S, Bigault O, Kearns LS, Boon M-Y et al. (2014) What is the appropriate age cut-off for cycloplegia in refraction. Acta ophthalmologica 92 (6): e458–62. https://doi.org/10.1111/aos.12388 PMID: 24641244
27. Fotedar R, Rochtchina E, Morgan I, Wang JJ, Mitchell P et al. (2007) Necessity of cycloplegia for assessing refractive error in 12-year-old children: a population-based study. American journal of ophthalmology 144 (2): 307–309. https://doi.org/10.1016/j.ajo.2007.03.041 PMID: 17659966
28. Lebow KA, Campbell CE (2014) A comparison of a traditional and wavefront autorefraction. Optometry and vision science: official publication of the American Academy of Optometry 91 (10): 1191–1198.
29. Bennett JR, Stalboerger GM, Hodge DO, Schornack MM (2015) Comparison of refractive assessment by wavefront aberrometry, autorefraction, and subjective refraction. Journal of optometry 8 (2): 109–115. https://doi.org/10.1016/j.optom.2014.11.001 PMID: 25498534
30. He M, Zeng J, Liu Y, Xu J, Pokharel GP et al. (2004) Refractive error and visual impairment in urban children in southern china. Investigative ophthalmology & visual science 45 (3): 793–799.
31. Williams KM, Verhoeven VJM, Cumberland P, Bertelsen G, Wolfram C et al. (2015) Prevalence of refractive error in Europe: the European Eye Epidemiology (E(3)) Consortium. European journal of epidemiology 30 (4): 305–315. https://doi.org/10.1007/s10654-015-0010-0 PMID: 25784363
32. Wellington J (1992) Teaching and learning in a Chinese primary school. Education 3–13 20 (2): 8–10.
33. Tideman JWL, Polling JR, Vingerling JR, Jaddoe VWV, Williams C et al. (2017) Axial length growth and the risk of developing myopia in European children. Acta ophthalmologica 96 (3): 301–309. https://doi.org/10.1111/aos.13603 PMID: 29265742
34. Kim DH, Lim HT (2019) Myopia Growth Chart Based on a Population-Based Survey (KNHANES IV-V): A Novel Prediction Model of Myopic Progression in Childhood. Journal of pediatric ophthalmology and strabismus 56 (2): 73–77. https://doi.org/10.3928/01913913-20181003-01 PMID: 30371914
35. Rauscher FG, Lange H, Yahiaoui-Doktor M, Tegetmeyer H, Sterker I et al. (2019) Agreement and Repeatability of Noncycloplegic and Cycloplegic Wavefront-based Autorefraction in Children. Optometry and vision science: official publication of the American Academy of Optometry 96 (11): 879–889.

Longitudinal analysis of axial length growth in a German cohort of healthy children and adolescents

OPO OPHTHALMIC & PHYSIOLOGICAL OPTICS
THE JOURNAL OF THE COLLEGE OF OPTOMETRISTS

Ophthalmic and Physiological Optics ISSN 0275-5408

Longitudinal analysis of axial length growth in a German cohort of healthy children and adolescents

Carolin Truckenbrod[1], Christof Meigen[1], Manuela Brandt[1], Mandy Vogel[1], Pablo Sanz Diez[2,3], Siegfried Wahl[2,3], Anne Jurkutat[1] and Wieland Kiess[1,4,5]

[1]Leipzig Research Center for Civilization Diseases (LIFE), Leipzig University, Leipzig, Germany, [2]Institute for Ophthalmic Research, Eberhard Karls University Tuebingen, Tuebingen, Germany, [3]Carl Zeiss Vision International GmbH, Aalen, Germany, [4]Department of Women and Child Health, University Hospital for Children and Adolescents and Center for Pediatric Research, Leipzig University, Leipzig, Germany, and [5]Center for Pediatric Research, Leipzig University, Leipzig, Germany

Citation information: Truckenbrod C, Meigen C, Brandt M, Vogel M, Sanz Diez P, Wahl S, Jurkutat A, & Kiess W. Longitudinal analysis of axial length growth in a German cohort of healthy children and adolescents. *Ophthalmic Physiol Opt*. 2021. https://doi.org/10.1111/opo.12817

Keywords: axial length, emmetropia, growth charts, hyperopia, myopia, prevalence curves

Correspondence: Carolin Truckenbrod
E-mail address: carolin.truckenbrod@t-online.de

Received: 7 December 2020; Accepted: 5 March 2021

Abstract

Purpose: To generate continuous growth curves for axial length (AL) in German children. We hypothesise that percentile curves of AL can be used as a predictive measure of myopia.

Methods: In this longitudinal and cross-sectional LIFE Child Study, children's non-cycloplegic refraction data was collected using the Zeiss i.Profiler plus while AL was measured using the Haag-Streit Lenstar. Reference growth curves were estimated as a continuous non-parametric function of age.

Results: Data from 4511 visits of 1965 participants (1021 boys and 944 girls) between 3 and 18 years of age were analysed. For all ages and percentiles, the estimated AL was higher in boys than girls. AL differences between boys and girls were most pronounced in the 98th percentile at 3 years of age, being 0.93 mm longer eyes in boys. This difference decreased to 0.21 mm at 18 years of age. While the lower percentiles of AL reach their final value around age 13, the 50th percentile was still increasing by 0.05 mm per year until the end of the observation period. While, in general, children with longer eyes are more likely to develop myopia, this relationship is weaker between the ages of 5 and 8.

Conclusion: The LIFE Child Study data provides European AL data. In both Germany and China, AL has comparable growth rates when the baseline ALs are compared as percentiles. Thus, percentile curves of AL can be used as a predictive measure for the likelihood of developing as well as the progression of myopia.

Introduction

At birth, infants show a wide range of refractive errors, roughly following a Gaussian distribution.[1] Up to 6 years of age, the emmetropization process can be observed.[2] This is a mechanism to control eye growth in order to become emmetropic or a low hyperope. Beyond the age of 6 years, the trend changes in many populations. Stable refraction is often followed by a myopic shift, which slows down after some years and asymptotes towards a stable myopic refraction.[3]

At birth, the eye is approximately 17 mm long, and generally grows to about 23 mm in adolescence.[4] The elongation is greatest during the first year of life, with decreasing growth rates towards the end of this first year. Jin *et al*. describe the axial length growth as a logarithmic function, which asymptotes towards the final length. Their final observed length was 24.35 mm at 15 years. At this age, most of the children in their population were myopic.[5] These data originate from a cohort of Chinese children of all refractive states. Therefore, their final AL does not represent a common end point of low hyperopia, but axial elongation due to myopia development.[6] Hence, the assessment of AL is heavily dependent on the underlying population and the respective prevalent conditions must be taken into account, so this final AL cannot necessarily be adapted to other ethnicities.

Hashemi *et al.* reported that AL is gender-dependent, with longer eyes in boys. Interestingly, the growth rate in their study showed accelerations for boys between 8–10 years and 14–16 years of age, and for girls between 6–7 years and 11–13 years of age. After 14 years, only small changes were observed in either group, and these may be due to myopia development.[7]

The prediction of myopia development and mechanisms to control myopia progression are of increasing scientific interest,[8,9] mainly due to the increasing prevalence of myopia, especially in east Asia but also in other countries.[10] In combination with the success that has been achieved in slowing myopia progression, for example with atropine eye drops and orthokeratology, a method needs to be developed to predict future myopia progression in the eyes of children.[11]

Axial growth rates are higher in new myopes, but also before myopia onset in children who later go on to became myopic.[12] There is a strong correlation between myopia and axial length, and yet axial length increases disproportionally to myopia at the beginning. Due to the emmetropization processes, excessive elongation of the eye may be compensated by an increased rate of decline of lens power in the early phase.[12,13] Breslin *et al.* showed that axial elongation between 6–10 years of age is higher than that between 12–16 years.[14]

While there is data concerning axial elongation in the growing eye with respect to myopia development for Asian populations,[8,15,16,5,17] there is little data for individuals in central Europe. Tideman *et al.* used a relatively new approach to predict myopia progression using centile curves. They combined data from three different studies conducted in England and the Netherlands (Generation R Study, Avon Longitudinal Study and Rotterdam Study III) with varying study populations, settings, instruments and methods, as well as different birth years which could result in a different prevalence of myopia.[9] However, AL data were only available for the ages of 6, 9 and 15 years.

Therefore, there is a lack of continuous data showing axial elongation in the growing eye of central Europeans. This would allow the generation of more accurate centile curves for this population. Accordingly, this study aims to develop continuous growth curves showing axial length in German children. We hypothesise that percentile curves of axial length can be used as a predictive measure of myopia.

Methods

Study design

This analysis is part of the LIFE Child Study, which was approved by the Ethical Committee of the Medical Faculty of the University of Leipzig (Reg. No. 264-10-ek) and registered with the trial number NCT02550236. The study design has been described elsewhere.[18] The study site is in Leipzig, Germany.

Participants were invited to present once a year. At each visit, a consent form was signed by the parents and, from the age of 12 years, by the children. Data were analysed from 4511 visits of 1965 participants (1021 boys and 944 girls). Data were collected between 2014 and 2018.

There are ethical restrictions on sharing pseudonymised data sets. The LIFE Child Study collects potentially sensitive information. Publishing data sets is not covered by the informed consent provided by the study participants. Furthermore, the data protection concept of LIFE requests that all (external and internal) researchers interested in accessing data sign a project agreement. Researchers that are interested in accessing and analysing data collected in the LIFE Child Study may contact the data use and access committee (dm@life.uni-leipzig.de).

Measurements

AL was measured with the Lenstar (Haag-Streit, haag-streit.com) and was defined as the distance between the tear film and retinal pigment epithelium.[19] To conduct the measurement, the chin was placed on the chinrest, and the forehead was pressed against a strap. Participants gazed at a fixation light. For each patient, three measurements were obtained for each eye.

Refraction was measured three times in each eye in a darkened room without cycloplegia with the Zeiss i. Profiler plus (Carl Zeiss Vision GmbH, zeiss.com), which is based on a Hartmann-Shack sensor. The room was darkened to maximise pupil size. The refractive error was analysed for a 3 mm pupil and a vertex distance of 12 mm. Myopia was defined as a spherical equivalent <-0.75 D.

Statistical analysis

The World Health Organization (WHO) recommends constructing growth curves as a continuous age-varying distribution described by different parameters dependent on age.[20] Therefore, we applied generalised additive models for location, shape and scale as implemented in the R package GAMLSS (gamlss.com) to create reference curves, which was one of the WHO's favoured methods for modelling growth curves. We have used the same model to generate centile curves for refraction.[21] To facilitate the comparison with the results by Tideman *et al.* and Sanz Diez *et al.*, we present the 2^{nd}, 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th} and 98^{th} percentiles. To assess the relationship between refractive state as an outcome, eye length and age, we used a logistic regression model with the *z*-score of the eye length and a spline base of age with knots at 25%, 50% and 75% of the data as independent variables.

For AL, the median of all three measurements from the right eye was used for the estimation of the percentile curves. The spherical equivalent (SE) refractive error of the right eye was calculated as sphere + ½ cylinder power using the median result for the three measurements taken with the Zeiss i. Profiler plus.

The eye length growth was calculated from two consecutive measurements of the same proband, which were usually taken annually (equation 1). Measurement pairs less than 6 months or more than 1.5 years apart were excluded, and the AL change was assigned to the mean age of the two visits.

$$\text{Annual AL change} = \frac{(\text{eye length at 2nd visit} - \text{eye length at 1st visit}) * 365.25\ \text{days}}{\text{number of days between 1st and 2nd visit}} \quad (1)$$

Results

Correlation of axial length (AL) with spherical equivalent (SE)

Correlation coefficients for AL with the SE was $R^2 = 0.32$ and $R^2 = 0.37$ for boys and girls, respectively, with $p < 0.0001$ and $\beta = -0.43$ for boys and $\beta = -0.44$ for girls. For each dioptre change, AL was on average 0.43 mm/0.44 mm higher. The number of participants, divided into first and follow up visits for each age group, is shown in *Table 1*. This also shows myopia prevalence, which increases with age.

Table 1. Number of first and follow up visits for each age group and myopia prevalence

Age group [years]	First visits	Follow up visits	Myopia prevalence	95% confidence interval
2.89–2.99	4	0	0%	0%–60.24%
3.00–3.99	96	2	2.08%	0.25%–7.32%
4.00–4.99	239	36	3.04%	1.32%–5.91%
5.00–5.99	215	145	2.56%	1.18%–4.80%
6.00–6.99	167	191	3.16%	1.59%–5.59%
7.00–7.99	128	223	4.65%	2.68%–7.44%
8.00–8.99	124	218	3.90%	2.09%–6.58%
9.00–9.99	149	217	6.91%	4.52%–10.03%
10.00–10.99	130	219	11.11%	7.98%–14.93%
11.00–11.99	138	223	16.08%	12.35%–20.41%
12.00–12.99	171	204	18.68%	14.81%–23.07%
13.00–13.99	98	236	21.69%	17.37%–26.51%
14.00–14.99	92	209	22.79%	18.12%–28.02%
15.00–15.99	94	185	23.60%	18.63%–29.15%
16.00–16.99	78	135	26.42%	20.61%–32.89%
17.00–17.99	42	103	25.87%	18.92%–33.86%

Annual change in axial length (AL) with age

The mean annual change of the median AL was 0.3 mm per year in 3-year-old children. This decreased to 0.1 mm per year in 13+ year-old children (see *Figure 1*). The standard error for measurement of eye length was ±0.04 mm. While the 2nd and the 50th percentiles of annual AL change run almost on the same level from 7 years of age onwards for each gender, there are differences in the 98th centile. Here, boys show a higher yearly increase in AL between ages 3 and 9 compared with girls, and the trend changes from age 9 onwards. The 2nd centile is almost 0 for boys of all ages and decreases from 0.1 to 0 between the ages of 3 and 7 for girls. Hence, there are always some children with no change in AL between the two consecutive measurements.

Reference curves for axial length (AL) over age

Separate reference intervals for axial length with respect to age were created for boys and girls. *Figure S1* shows the 2nd, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 98th centiles of axial elongation with age from 3 to 18 years. The figure was created based on the method of Sanz Diez *et al.*[8] to allow easy comparison of the results from each study.

Figure 2 shows the percentile curves of AL for girls and boys on the left side and myopia prevalence as a function of age for each of the presented centiles on the right. The solid lines show the LIFE Child Study results. In comparison, the results of Sanz Diez *et al.* are shown as dashed lines. In the German cohort, for all ages and all percentiles calculated, AL was higher in boys compared with girls. In our data, the 2nd and 50th percentiles run almost parallel for each gender group. The difference in AL between boys and girls is highest for the 98th centile at 3 years of age, with boys having 0.91 mm longer eyes, although this difference decreases to 0.24 mm at 18 years of age. For both genders and all centiles, the increase in AL is highest between 3 and 11 years of age. In the 2nd centile, there is only marginal eye growth in boys and girls after the age of 13 years (less than 0.05 mm per year) and AL asymptotes towards its final length. For the 50th centile, the eye growth rate in boys and girls is about 0.05 mm per year from the age of 13 years up to the end of the observation period. In the 98th centile, growth rates are highest below the age of 11 years, but remain high up to the end of the observed period with rates of more than 0.1 and 0.15 mm per year for boys and girls, respectively, after 13 years of age.

Prevalence of myopia as a function of axial length (AL) (likelihood to develop myopia)

On the right side of *Figure 2*, the prevalence of myopia is shown as a function of AL centiles. This graph shows the

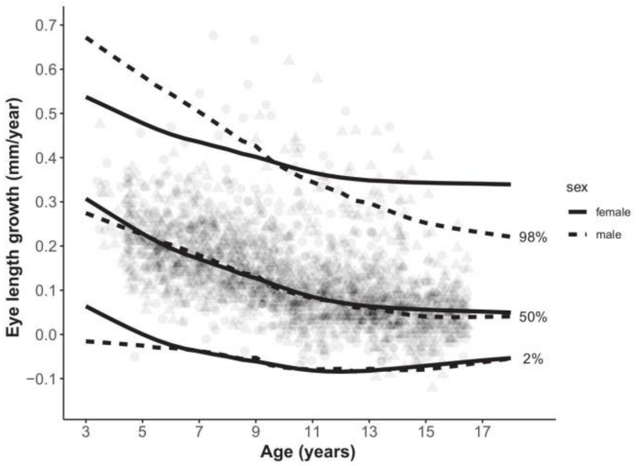

Figure 1. Annual axial length (AL) change in longitudinal data from the LIFE Child Study for girls (solid lines) and boys (dashed lines).

likelihood of having or developing myopia for a percentile of AL, as shown in the left hand graph. In the LIFE Child Study at 16 years of age, 2% and 6% of boys and girls, respectively, reached myopic refractive values of more than 0.75 D in the 5th centile. On the other hand, the 95th centile shows that 64% of boys and 59% of girls developed myopia by 16 years of age. Between 3 and 5 years of age, the likelihood of having myopia increases with age, especially above the 50th centile of AL, independent of gender. For the 95th centile, at 3 years of age 5% of males and 4% of females developed myopia, and by age 5 the prevalence has increased to 16% and 8% for boys and girls, respectively. From 5 to 7 years of age, an inverse trend is observed in the boys' AL centiles, where myopia prevalence decreased compared with the range between 3 and 5 years of age. However, the most pronounced differences are located in the higher centiles. At age 7, 11% of boys are myopic in the 95th centile. For girls, a plateau is reached between ages 5 and 7, with a relatively stable likelihood of being myopic across all centiles. Above 7 years of age, the trend is reversed again and myopia prevalence increases with age for all centiles of AL in both boys and girls. Thus, the increase of myopia prevalence is greater in the higher centiles of axial length. Especially between 8 and 12 years of age, the prevalence increases rapidly with age in the 75th, 90th and 95th centiles for girls, and the 90th and 95th centiles for boys.

Discussion

The decrease in myopia as a function of AL percentiles for boys might be due to the fact that there are relatively few children with myopia in each percentile, due to the low prevalence of myopia at this age. Accordingly, small fluctuations could cause this observation. At a younger age, the measurement error due to findings being obtained without cycloplegia is likely higher than with older children, and could cause fluctuations in responses.[22]

The relatively stable, reverse trend of myopia prevalence between 5 and 7 years of age could be explained by the findings of Rozema *et al.* They noted that AL elongation can be observed before myopia onset.[12] Between 5 and 8 years of age, the AL was increased in some children, although myopia had not yet developed. After 8 years of age, myopia onset can be measured in most of the children, and therefore, the association between the AL centile and myopia prevalence increased.

Correlation of axial length (AL) with spherical equivalent (SE)

In a cohort from Northern Ireland, McCullough *et al.* found an annual AL change of 0.12 mm in the 50th centile of AL (0.11 in the 1st centile and 0.15 in the 99th centile) in children between 6 and 16 years of age. However, their AL measurements were not analysed continuously with age, but categorized into four age groups. Therefore, a direct comparison of data is not possible.[23] However, their observed annual change is comparable to the annual change in AL of the present investigation in 6 to 16 year old children, which was 0.115 mm per year in the 50th centile, averaged across both genders.

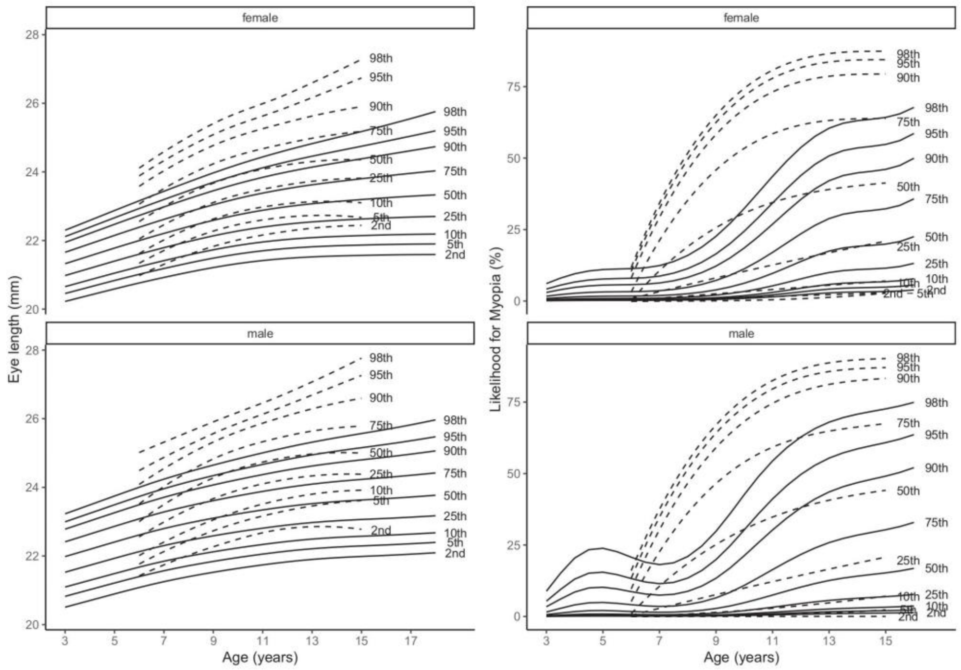

Figure 2. Left: Continuous centile curves of axial length with respect to age for the LIFE Child Study. Right: Prevalence of myopia as a function of the axial length centiles. Red and blue curves indicate data from girls and boys, respectively. The solid lines show the LIFE Child Study results (Germany) while the dashed lines indicate findings from a cohort in Wuhan, China.[8]

Axial length (AL) in comparison to other studies from Europe and China

In Europe, Tideman *et al*. were the first to estimate AL centile curves.[9] They presented combined data from three different study cohorts, two of which examined axial length in children. Data on 6- and 9-year old children were collected in the Netherlands, and data on 15-year-old children were collected in the UK. The 50th centiles of our data are very similar to those presented by Tideman *et al.*, as can be seen in *Table 2*. This underlines that boys have, in general, longer eyes than girls.

As the age-conditional distributions of ALs for 6-, 9- and 15- year-old children are very similar to the data from Tideman *et al*., our findings are likely to reflect central European populations. Therefore, they complement the results of Tideman *et al.*, as those authors analysed specific time points, but not continuous data covering the entire age span, from 3 to 18 years.

Whereas the LIFE Child Study data is very similar to other findings collected in central Europe, they differ from results obtained in China. The cohort analysed by Sanz Diez *et al.*[8] from the city of Wuhan included 5 to 16 year old children. At 5 years of age, the differences in mean AL between ethnicities were 0.39 mm in girls and 0.30 mm in boys, as shown in *Table 3*, which might be due to axial elongation in Chinese preschool children prior to developing myopia. This difference increased up to the age of 16 years, with about a 1.5 mm difference being found in boys and girls. At 5 years of age, the myopia prevalence in the Wuhan cohort was 4.00% and 6.32% for girls and boys, respectively. This increased to 87.93% and 93.44% of 16 year old girls and boys, respectively. At 5 years of age, myopia prevalence in the LIFE Child Study cohort was 4.70% for both genders, which is similar to the results from Sanz Diez *et al.* This subsequently increased to 28.40% at the age of 18, which is substantially less than the Wuhan cohort.

As AL is linked with refractive error, the longer eyes seen in China are consistent with the higher local prevalence of myopia.[12] However, at the age of 5 years, there is only a small difference in the prevalence of myopia between the LIFE Child Study cohort and the Chinese cohort, and yet a difference in

Table 2. 2nd, 25th, 50th, 75th and 98th centiles of axial length of children aged 6, 9, 12 and 15 years in China and Europe

		Female			Male		
	Percentile	LIFE Child Germany	Tideman *et al.*[9] Europe	Sanz Diez *et al.*[8] China	LIFE Child Germany	Tideman *et al.*[9] Europe	Sanz Diez *et al.*[8] China
6 years	2	20.76	–	20.97	21.08	–	21.44
	25	21.6	21.66	22.03	22.13	22.14	22.55
	50	22.00	22.06	22.54	22.61	22.59	22.99
	75	22.39	22.49	23.04	23.08	23.01	23.50
	98	23.16	–	24.07	24.00	–	25.00
9 years	2	21.21	–	21.86	21.53	–	22.21
	25	22.14	22.33	23.16	22.59	22.83	23.70
	50	22.59	22.79	23.72	23.10	23.31	24.32
	75	23.04	23.25	24.31	23.61	23.79	24.89
	98	23.97	–	25.55	24.65	–	25.96
12 years	2	21.48	–	22.24	21.83	–	22.86
	25	22.48	–	23.57	22.90	–	24.21
	50	22.99	–	24.16	23.44	–	24.83
	75	23.51	–	24.76	24.00	–	25.44
	98	24.64	–	26.13	25.17	–	26.70
15 years	2	21.57	–	22.45	21.99	–	22.76
	25	22.63	22.68	23.83	23.06	23.17	24.39
	50	23.19	23.15	24.37	23.63	23.65	25.01
	75	23.8	23.65	25.20	24.23	24.21	25.80
	98	25.18	–	27.32	25.57	–	27.78

Data from Europe comprise findings from the present study (LIFE child) as well as the results of Tideman *et al.* (countries: The Netherlands and UK).[9] Data from China are from Sanz Diez *et al.* (Wuhan, China).[8]

AL can already be observed. This is in line with the findings of Rozema *et al.* showing that axial elongation can be observed before myopia onset.[12] Consequentially, in younger children, the ALs in both ethnicities are likely to be similar, as shown by Lu *et al.*, who examined the AL of a cohort of Chinese children from the Shandong province.[17] The respective data was collected from children aged ≥ 4 years. *Table 3* shows increasing differences between ethnicities with age. In general, the Shandong cohort exhibits longer eyes than the LIFE Child Study cohort, but shorter axial lengths than the Wuhan subjects.[8] This might be due to the inclusion of children from both rural and urban regions, with the children from rural areas having shorter eyes.[17] In a cohort of 3-year-old children in Singapore, consisting of 55% Chinese, 26.1% Malay and 18.9% Indian children, Foo *et al.* recorded a mean AL of 21.73 mm for both genders,[24] whereas in our study population, the mean axial length at 3 years of age was 21.86 mm. These results also support the hypothesis of similar ALs in very young Chinese and German children.

Comparison of the likelihood to develop myopia depending on axial length (AL) in China and Germany

Sanz Diez *et al.* also published findings on myopia prevalence as a function of AL from the Wuhan cohort.[8] Their data presents a continuously increasing prevalence of myopia for each centile of AL up to 12 years of age, as shown by the dashed lines in *Figure 2* (right). Thereafter, the prevalence of myopia in girls remained stable for each centile of AL until age 15. However, for boys, a further increase in myopia prevalence could be observed. While our model included age as a continuous explanatory variable, Sanz Diez *et al.* estimated myopia prevalence for the discrete age groups of 6, 9, 12 and 15 years. Therefore, it cannot be excluded that a weaker relationship between myopia prevalence and AL for a specific age group could be found if the data was analysed accordingly. A dip in the prevalence of myopia (as a function of AL) at 8 years of age may be present in China (as was observed here), but this is not verifiable due to a lack of data.

As the prevalence and the degree of myopia is much higher in China than Germany, the association between higher centiles of AL with myopia will be stronger in China. For both sexes, the 75th centile of AL in China is comparable to the 98th centile in Germany. For example, at 6 years of age, the 75th AL centile in Chinese girls is 23.04 mm, which corresponds approximately to the 98th centile (23.16 mm) in German girls. At the age of 15, the same percentiles correspond to an AL of 25.20 and 25.18 mm in Chinese and German girls, respectively. The same observations are true in boys, that is the 75th centile for boys and girls in Germany is comparable to the 25th centile in the

Table 3. 50th centile of axial length (AL) for children in the LIFE Child Study in Germany and two cohorts in China

	AL Female 50th centile			AL Male 50th centile		
Age (years)	Germany	China, Wuhan[8]	China, Shandong[17]	Germany	China, Wuhan[8]	China, Shandong[17]
3	21.33	–	–	21.98	–	–
4	21.55	–	21.96	22.20	–	22.30
5	21.78	22.17	22.02	22.41	22.71	22.52
6	22.00	22.56	22.25	22.61	23.03	22.65
7	22.21	22.84	22.39	22.80	23.31	23.04
8	22.41	23.40	22.83	22.96	23.88	23.28
9	22.59	23.73	23.04	23.10	24.26	23.61
10	22.75	23.92	23.29	23.23	24.44	23.88
11	22.88	24.15	23.54	23.34	24.69	23.97
12	22.99	24.16	23.69	23.44	24.82	24.14
13	23.07	24.29	23.81	23.53	24.81	24.37
14	23.14	24.44	24.17	23.59	24.96	24.69
15	23.19	24.50	24.36	23.63	25.15	24.63
16	23.25	24.73	24.57	23.67	25.19	24.76
17	23.29	–	24.43	23.72	–	24.81
18	23.33	–	24.27	23.77	–	24.69

The cohort in the city of Wuhan covered the urban region,[8] while the Shandong study included both rural and urban regions.[17]

Chinese data. Even though the AL graphs of the two countries are labelled with different centiles, they run approximately parallel at an equivalent level. Although AL increases slightly faster in China than Germany between 6 and 9 years of age, in general, the graphs run almost parallel afterwards for all percentiles.

At the age of 15 years, approximately 64% of German girls in the 98th centile and 68% at the 75th centile in China are myopic (for German boys 73% and Chinese boys 63%). Hence, the link between AL (in absolute numbers) and the likelihood of myopia seems to be very similar in both ethnicities. At the age of 6 years, approximately 11% of German girls at the 98th centile and 3% of Chinese girls at the 75th centile are myopic. This difference in these younger age groups may be because refraction data in China was obtained under cycloplegia whereas cycloplegia was not used in our study. In younger children, this would lead to an overestimation of myopia in Germany.[22] When comparing the graphs one must consider that the smoothed curves from the study by Sanz Diez *et al.*[8] consist of only three measurement points, whereas the LIFE Child Study delivers more precise curves with continuous data across ages. The 98th German centile and the 75th Chinese can be compared in *Table 2*. For the lower centiles, which run on the same level, the link between AL and likelihood of myopia was weaker. For example, the 50th centile of AL in China and the 90th centile in Germany run almost on the same level. At this centile, at age 15, 46% of Germany girls (49% boys) are myopic as are 44% of Chinese girls (40% boys). The 25th centile of AL in China and the 75th centile in Germany also run parallel. However, while in China approximately 20% of girls at the 25th AL centile are myopic by age 15, in Germany, the prevalence reaches 32% at the 75th AL percentile for the same age (19% of boys in China and 30% in Germany). Therefore, at this centile with relatively few expected myopic children, the probability of myopia has likely been overestimated in Germany due to the lack of cycloplegia.

Limitations

At the higher AL percentiles, and thus likely myopia cases (as a function of AL), the number of children included here is small. Sample sizes varied in each age group, as well as between genders, and that may affect the percentiles and prevalence of myopia. One would also expect a similar development in the likelihood of becoming myopic in girls and boys up to 7 years of age. For these younger age groups it is desirable to gather more data from larger cohorts to improve the curves and the predictive values for the likelihood of myopia.

In addition, we did not use cycloplegia to measure refraction. Rauscher *et al.* showed that the SE measured with the Zeiss i. Profiler plus was 0.55 D lower without cycloplegia compared with the cycloplegic refraction.[25] Thus, it is likely that myopia was overestimated in the present investigation. However, this bias is similar across refractive states, as shown by Rauscher *et al.* Therefore, it should have no influence on the centile curves of AL with age. The prevalence of myopia for each AL centile as a function of age is likely to have been overestimated compared with a cycloplegic refraction. Additionally, the difference between cycloplegic and non-cycloplegic refraction is higher in younger children and but reduced in older children.[22] Therefore, a limitation of our study is the prediction of myopia prevalence in the younger age groups and the lower centiles with few myopia cases. For older ages and higher centiles, predictions of the likelihood of myopia should become more accurate.

While AL is the most important determinant of myopia, it is not the only parameter involved in refractive error development. The principal determinant of myopic maculopathy in adults is not necessarily a refractive error less than −5.0 D, but rather an AL exceeding 25.3 mm in women and 25.9 mm in men.[26] In cases with long ALs but no or little myopia, the cornea is flatter. Therefore, to understand the relationship between refractive error and AL, corneal power should also be considered. While analysing this aspect is beyond the scope of this paper, we will consider a complementary paper showing AL curves for different corneal powers. Additionally, while the LIFE Child Study and Sanz Diez *et al.*[8] used the Lenstar biometry device, Lu *et al.*[17] and Foo *et al.*[24] used the IOLMaster to measure AL. In an adult population, there is a measurement difference of approximately 0.01 mm between the two devices, with the IOLMaster showing slightly longer AL measurements. However, this measurement difference is clinically insignificant.[19]

Conclusion

In general, AL is longer in boys than girls. This difference is greater for the higher centiles and in younger children. While the lower AL centiles asymptote towards the final AL after 13 years of age, there is a small continuous growth in the 50^{th} centile of 0.05 mm per year from the age of 13 years up to the end of the observation period. In the higher centiles, there is an even higher annual increase in AL for both boys and girls.

Children with longer eyes are more likely to develop myopia. The likelihood of developing myopia increases in general with age. This relationship is weaker between the ages of 5 and 8 years. This might be due to the onset of school myopia, which can be observed as increased AL first, before myopia becomes manifest. Some years after increased elongation of the eye, children start to exhibit myopia. This supports the findings of Rozema *et al.*, who showed that an increase in AL can be observed before the onset of myopia.[12]

The results of this investigation are very similar to the findings of a previous European study.[9] However, our data stems from a single cohort and was analysed as continuous data.[9]

When comparing our data with findings from China, the ALs are similar in children around 3 years of age.[24] Thereafter, the ALs in China become longer with age compared to those in Germany. If only children with the same AL are compared, then the state of refraction is very similar for each ethnicity at the higher centiles.[22] It would be of interest to compare the likelihood of developing myopia in different ethnicities for equivalent centiles of AL using the same refractive test methods.

This study supports and implements the application of centile curves of AL as a predictive measure of the likelihood for the development and progression of myopia. Therefore, these data, as the first European dataset over the entire age span of 3–18 years, are highly relevant for the early detection of myopia.

Acknowledgements

The authors are very grateful to all the families who have taken part in this study. The authors wish to thank the whole LIFE Child Study Team for their contributions to this work. This publication is supported by LIFE Leipzig Research Center for Civilization Diseases, Leipzig University. LIFE is funded by the European Union, the European Social Fund (ESF), the European Regional Development Fund (ERDF, grant number 100232872), and by the Free State of Saxony within the framework of the excellence initiative.

Conflict of interest

S. Wahl and P. Sanz Diez are employees of Carl Zeiss Vision International GmbH; however, none of the authors has any financial or conflicting interests concerning the content of this research, which was conducted following the rules of neutral scientific practice.

Author contributions

Carolin Truckenbrod: Conceptualization (equal); Data curation (supporting); Investigation (equal); Methodology (equal); Writing-original draft (lead); Writing-review & editing (lead). **Christof Meigen:** Conceptualization (equal); Formal analysis (equal); Methodology (equal); Software (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Manuela Brandt:** Data curation (lead); Writing-review & editing (supporting). **Mandy Vogel:** Methodology (equal); Software (equal); Writing-review & editing (equal). **Pablo Sanz Diez:** Writing-review & editing (equal). **Siegfried Wahl:** Supervision (equal); Writing-review & editing (equal). **Anne Jurkutat:** Investigation (equal); Resources (equal). **Wieland Kiess:** Funding acquisition (equal); Project administration (equal); Resources (equal); Supervision (equal).

References

1. Pennie FC, Wood ICJ, Olsen C, White S & Charman WN. A longitudinal study of the biometric and refractive changes in

full-term infants during the first year of life. *Vision Res* 2001; 41: 2799–2810.
2. Flitcroft DI. Emmetropisation and the aetiology of refractive errors. *Eye* 2014; 28: 169–179.
3. McBrien NA & Adams DW. A longitudinal investigation of adult-onset and adult-progression of myopia in an occupational group. Refractive and biometric findings. *Invest Ophthalmol Vis Sci* 1997; 38: 321–333.
4. Kaufman PL, Levin LA & Adler FH, editors. *Adler's Physiology of the Eye: Expert Consult*; Activate at expertconsult.com; searchable full text online. 11th edn. Saunders Elsevier: Edinburgh, 2011.
5. Jin P, Li M, He X *et al.* Anterior-chamber angle and axial length measurements in normal Chinese children. *J Glaucoma* 2016; 25: 692–697.
6. Wu P-C, Huang H-M, Yu H-J, Fang P-C & Chen C-T. Epidemiology of myopia. *Asia Pac J Ophthalmol* 2016; 5: 386–393.
7. Hashemi H, Jafarzadehpur E, Ghaderi S *et al.* Ocular components during the ages of ocular development. *Acta Ophthalmol* 2015; 93: e74–e81.
8. Sanz Diez P, Yang L-H, Lu M-X, Wahl S & Ohlendorf A. Growth curves of myopia-related parameters to clinically monitor the refractive development in Chinese schoolchildren. *Graefes Arch Clin Exp Ophthalmol* 2019; 257: 1045–1053.
9. Tideman JWL, Polling JR, Vingerling JR *et al.* Axial length growth and the risk of developing myopia in European children. *Acta Ophthalmol* 2018; 96: 301–309.
10. Foster PJ & Jiang Y. Epidemiology of myopia. *Eye* 2014; 28: 202–208.
11. Bullimore MA & Brennan NA. Myopia control: why each diopter matters. *Optom Vis Sci* 2019; 96: 463–465.
12. Rozema J, Dankert S, Iribarren R, Lanca C & Saw S-M. Axial growth and lens power loss at myopia onset in Singaporean children. *Invest Ophthalmol Vis Sci* 2019; 60: 3091–3099.
13. Mutti DO, Hayes JR, Mitchell GL *et al.* Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. *Invest Ophthalmol Vis Sci* 2007; 48: 2510–2519.
14. Breslin KMM, O'Donoghue L & Saunders KJ. A prospective study of spherical refractive error and ocular components among Northern Irish schoolchildren (the NICER study). *Invest Ophthalmol Vis Sci* 2013; 54: 4843–4850.
15. Iribarren R, Morgan IG, Chan YH, Lin X & Saw S-M. Changes in lens power in Singapore Chinese children during refractive development. *Invest Ophthalmol Vis Sci* 2012; 53: 5124–5130.
16. Bhardwaj V & Rajeshbhai GP. Axial length, anterior chamber depth-a study in different age groups and refractive errors. *J Clin Diagn Res* 2013; 7: 2211–2212.
17. Lu TL, Wu JF, Ye X *et al.* Axial length and associated factors in children: the Shandong Children Eye Study. *Ophthalmologica* 2016; 235: 78–86.
18. Poulain T, Baber R, Vogel M *et al.* The LIFE Child study: a population-based perinatal and pediatric cohort in Germany. *Eur J Epidemiol* 2017; 32: 145–158.
19. Wang X-G, Dong J, Pu Y-L, Liu H-J & Wu Q. Comparison axial length measurements from three biometric instruments in high myopia. *Int J Ophthalmol* 2016; 9: 876–880.
20. Borghi E, de Onis M, Garza C *et al.* Construction of the World Health Organization child growth standards: selection of methods for attained growth curves. *Stat Med* 2006; 25: 247–265.
21. Truckenbrod C, Meigen C, Brandt M *et al.* Reference curves for refraction in a German cohort of healthy children and adolescents. *PLoS One* 2020; 15: e0230291.
22. Sankaridurg P, He X, Naduvilath T *et al.* Comparison of noncycloplegic and cycloplegic autorefraction in categorizing refractive error data in children. *Acta Ophthalmol* 2017; 95: e633–e640.
23. McCullough S, Adamson G, Breslin KMM *et al.* Axial growth and refractive change in white European children and young adults: predictive factors for myopia. *Sci Rep* 10: 1–13.
24. Foo VHX, Verkicharla PK, Ikram MK *et al.* Axial length/-corneal radius of curvature ratio and myopia in 3-year-old children. *Transl Vis Sci Technol* 2016; 5: 5. tvst.arvojournals.org/article.aspx?articleid=2491458 (Accessed 23/03/21).
25. Rauscher FG, Lange H, Yahiaoui-Doktor M *et al.* Agreement and repeatability of noncycloplegic and cycloplegic wavefront-based autorefraction in children. *Optom Vis Sci* 2019; 96: 879–889.
26. Hashimoto S, Yasuda M, Fujiwara K *et al.* Association between axial length and myopic maculopathy: the Hisayama Study. *Ophthalmol Retina* 2019; 3: 867–873.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Left: Continuous centile curves of axial length over age of the LIFE Child study. Right: Prevalence of Myopia as a function of the axial length centiles. The solid lines show the LIFE Child results (Germany) and the dashed lines the results form a cohort in Wuhan, China.[12]

Zusammenfassung der Arbeit

Kumulative Dissertation zur Erlangung des akademischen Grades

Dr. rer. med.

Refractive and axial development of the growing eye

eingereicht von Carolin Truckenbrod

angefertigt an / in Medizinische Fakultät der Universität Leipzig

betreut von Prof. Dr. med. Wieland Kiess/ Christof Meigen

Mai 2021

Summary

This thesis aimed to illustrate and describe the current status of refraction and axial length in German children and adolescents. In contrast to previous studies growth curves were generated, instead of analysing myopia prevalence at separate age groups. This allows for an easier understanding and comparison of eye development.

Myopia prevalence in the LIFE Child cohort

In a first step the current status of refraction and myopia prevalence for children in Germany was defined. The hypothesis was, that myopia prevalence in the LIFE Child study is comparable to other German and European paediatric cohorts.

In the LIFE Child study the myopia prevalence from children aged 3 to 16 years is overall 10.8%. This is even less than in the KiGGS survey, where the overall myopia prevalence was 13.3% in children aged 3 to 17 years. For the individual age groups a similar trend towards increasing myopia prevalence with increasing age could be observed in both study cohorts.[4] The results of the LIFE Child study cohort are also comparable to the NICER study in the UK.[44] Higher prevalences of myopia were found in Sweden. There myopia prevalence in children aged 12 and 13 years was 49.7%.[45]

In China myopia and high myopia is an increasing public health issue with prevalences of high myopia of more than -6.0 D in 1.8% of Hong Kong Chinese schoolchildren aged 6 to 12 years [46] and 4.3% of Chinese children from Beijing aged 7 to 18 years.[47] High myopia with over -6.0 D was found in only 0.03 % of children in the LIFE Child cohort.

It was shown, that myopia prevalence in the LIFE Child study cohort is comparable to other German and European studies observing refraction in Children. High myopia, which increases the risks for eye diseases, such as myopic maculopathy and retinal detachment, is much lower in Germany compared to China.

Centile curves of refraction in Germany in comparison to Chinese reference intervals

In a second step percentiles for refraction over age were generated. The hypothesis was, that the development of refractive error in China diverges from LIFE Child reference group around the age of school enrolment, and the difference is larger for the lower centiles.

When comparing reference curves of refraction in Germany and China only little differences can be found up to the age of 5 years. Thereafter increasing differences can be seen with increasing age. While the differences in the 3rd percentile increase dramatically between the age of 6 and 15 years, only subtle differences were observable in the 97th percentile. For both populations the myopia progression rates increase with higher baseline myopia.[29]

It was shown, that the development of refractive error in China and Germany diverge around school enrolment. The difference was larger for the lower centiles.

In order to use these centile curves in paediatric practice the predictive value of the LIFE Child percentile curves needs to be defined. Since no cycloplegia was applied the reliability of the measurements was not high enough to obtain predictive values from the current longitudinal data. The standard error in the measurement of spherical equivalent was ±0.78 D. The annual mean change of the spherical equivalent was 0.05D. The observation period was 4 years, thus resulting in a mean change of spherical equivalent of 0.2 D throughout the study period. Therefore, a longitudinal analysis of the development of refraction is currently impossible. A longer period of observation or the application of cycloplegia throughout the measurements would be required to obtain reliable predictive values.

Centile curves of axial length as an indicator for myopia risk

In the third step percentile curves for axial length over age were generated. The hypothesis was, that eye length can be reliably measured, and reference curves for eye length development can be used to identify children with high risk for myopia.

The standard error in the measurement of eye length with the LENSTAR was ± 0.04mm. The mean annual change of the median axial length was 0.3 mm, thus being much higher than the standard error. This shows, that the eye length can be reliably measured and analysis of longitudinal data is possible.

The percentile curves of axial length show, that the lower centiles asymptote towards the final axial length from the age of 13 years. In the higher centiles a continuous annual increase in axial length can be observed. Children with longer eyes are more likely to develop myopia. This supports the application of centile curves of axial length as a predictive measure for the likelihood to develop and progression of myopia. Data could be even further improved if cycloplegia was applied to determine refraction.

In comparison to Chinese data there are only little differences at 3 years of age. With increasing age eyes in Germany are shorter. Interestingly the likelihood of myopia is similar in both ethnicities, if only children with the same axial length are compared.

The centile curves of refraction derived from the LIFE child study cohort can be used to identify children with risk for myopia.

Conclusion

A current approach to analyse myopia progression and determine the risk for myopia in individuals is the use of centile curves. The first centile curves of refraction in Europe were generated from the LIFE Child data. Centile curves of axial length from the LIFE Child study confirm and complete existing European axial growth curves.

Prospect

In order to reduce measurement errors and gain more accurate and comparable data of refraction the autorefraction in the LIFE child study should be carried out in cycloplegia. This would improve data quality tremendously and add significant value to future analysis of refractive data. Especially longitudinal observations will then be more accurate. Interventions in refractive development, such as Orthokeratology and Atropine, will become more common and should be analysed in future. The Corona crisis offers a unique chance to study the impact of increased screen- and near work time on axial length and refraction. Analysis of the development of axial length and refraction in 2020 and 2021 in comparison to previous years should be carried out in future.

References

1 Steffen C. E. Schmidt, Bastian Anedda, Alexander Burchartz, et al. Physical activity and screen time of children and adolescents before and during the COVID-19 lockdown in Germany: a natural experiment. *Sci Rep*;10(1):1-12. doi:10.1038/s41598-020-78438-4.

2 Foster PJ, Jiang Y. Epidemiology of myopia. *Eye (Lond)*. 2014;28(2):202-208. doi:10.1038/eye.2013.280.

3 Wang J, Li Y, Musch DC, et al. Progression of Myopia in School-Aged Children After COVID-19 Home Confinement. *JAMA Ophthalmol*. 2021. doi:10.1001/jamaophthalmol.2020.6239.

4 Schuster AK, Elflein HM, Pokora R, Urschitz MS. Prävalenz und Risikofaktoren der Kurzsichtigkeit bei Kindern und Jugendlichen in Deutschland – Ergebnisse der KiGGS-Studie. *Klin Padiatr*. 2017;229(4):234-240. doi:10.1055/s-0043-102938.

5 Wu P-C, Huang H-M, Yu H-J, Fang P-C, Chen C-T. Epidemiology of Myopia. *Asia Pac J Ophthalmol (Phila)*. 2016;5(6):386-393. doi:10.1097/APO.0000000000000236.

6 Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res*. 2012;31(6):622-660. doi:10.1016/j.preteyeres.2012.06.004.

7 Bullimore MA, Brennan NA. Myopia Control: Why Each Diopter Matters. *Optom Vis Sci*. 2019;96(6):463-465. doi:10.1097/OPX.0000000000001367.

8 Mitchell P, Hourihan F, Sandbach J, Jin Wang J. The relationship between glaucoma and myopia. *Ophthalmology*. 1999;106(10):2010-2015. doi:10.1016/S0161-6420(99)90416-5.

9 Lim R, Mitchell P, Cumming RG. Refractive associations with cataract: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci*. 1999;40(12):3021-3026.

10 Pin-Chen Huang, Ya-Chuan Hsiao, Ching-Yao Tsai, et al. Protective behaviours of near work and time outdoors in myopia prevalence and progression in myopic children: a 2-year prospective population study. *British Journal of Ophthalmology*. 2020;104(7):956-961. doi:10.1136/bjophthalmol-2019-314101.

11 Walline JJ, Lindsley K, Vedula SS, Cotter SA, Mutti DO, Twelker JD. Interventions to slow progression of myopia in children. *Cochrane Database Syst Rev*. 2011;(12):CD004916. doi:10.1002/14651858.CD004916.pub3.

12 Leo SW. Current approaches to myopia control. *Curr Opin Ophthalmol*. 2017;28(3):267-275. doi:10.1097/ICU.0000000000000367.

13 Wei-Shan Tsai, Jen-Hung Wang, Cheng-Jen Chiu. A comparative study of orthokeratology and low-dose atropine for the treatment of anisomyopia in children. *Sci Rep*;10(1):1-8. doi:10.1038/s41598-020-71142-3.

14 BVKJ Service GmbH. Paed.plus - www.bvkj-service-gmbh.de. https://www.bvkj-service-gmbh.de/paedplus/. Accessed May 10, 2019.

15 Mutti DO, Hayes JR, Mitchell GL, et al. Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. *Invest Ophthalmol Vis Sci*. 2007;48(6):2510-2519. doi:10.1167/iovs.06-0562.

16 Lam AK, Chan R, Pang PC. The repeatability and accuracy of axial length and anterior chamber depth measurements from the IOLMaster. *Ophthalmic Physiol Opt*. 2001;21(6):477-483. doi:10.1046/j.1475-1313.2001.00611.x.

17 Sankaridurg P, He X, Naduvilath T, et al. Comparison of noncycloplegic and cycloplegic autorefraction in categorizing refractive error data in children. *Acta Ophthalmol*. 2017;95(7):e633-e640. doi:10.1111/aos.13569.

18 Hyvärinen L, Walthes R, Jacob N, Chaplin KN, Leonhardt M. Current Understanding of What Infants See. *Curr Ophthalmol Rep*. 2014;2(4):142-149. doi:10.1007/s40135-014-0056-2.

19 Carrara VI, Darakomon MC, Thin NWW, et al. Evaluation and Acceptability of a Simplified Test of Visual Function at Birth in a Limited-Resource Setting. *PLoS ONE*. 2016;11(6):e0157087. doi:10.1371/journal.pone.0157087.

20 Guo D-D, Wu J-F, Hu Y-Y, et al. Stereoacuity and Related Factors: The Shandong Children Eye Study. *PLoS ONE*. 2016;11(7):e0157829. doi:10.1371/journal.pone.0157829.

21 Almoqbel FM, Irving EL, Leat SJ. Visual Acuity and Contrast Sensitivity Development in Children: Sweep Visually Evoked Potential and Psychophysics. *Optom Vis Sci*. 2017;94(8):830-837. doi:10.1097/OPX.0000000000001101.

22 Mutti DO, Mitchell GL, Jones LA, et al. Axial growth and changes in lenticular and corneal power during emmetropization in infants. *Invest Ophthalmol Vis Sci*. 2005;46(9):3074-3080. doi:10.1167/iovs.04-1040.

23 Iribarren R, Morgan IG, Chan YH, Lin X, Saw S-M. Changes in lens power in Singapore Chinese children during refractive development. *Invest Ophthalmol Vis Sci*. 2012;53(9):5124-5130. doi:10.1167/iovs.12-9637.

24 Pennie FC, Wood IC, Olsen C, White S, Charman WN. A longitudinal study of the biometric and refractive changes in full-term infants during the first year of life. *Vision Res*. 2001;41(21):2799-2810.

25 Mayer DL, Hansen RM, Moore BD, Kim S, Fulton AB. Cycloplegic refractions in healthy children aged 1 through 48 months. *Arch Ophthalmol*. 2001;119(11):1625-1628.

26 Flitcroft DI. Emmetropisation and the aetiology of refractive errors. *Eye (Lond)*. 2014;28(2):169-179. doi:10.1038/eye.2013.276.

27 Kaufman PL, Levin LA, Adler FH, eds. *Adler's physiology of the eye: Expert consult ; activate at expertconsult.com ; searchable full text online.* 11. ed. Edinburgh: Saunders Elsevier; 2011.

28 Zadnik K, Sinnott LT, Cotter SA, et al. Prediction of Juvenile-Onset Myopia. *JAMA Ophthalmol*. 2015;133(6):683-689. doi:10.1001/jamaophthalmol.2015.0471.

29 Chen Y, Zhang J, Morgan IG, He M. Identifying Children at Risk of High Myopia Using Population Centile Curves of Refraction. *PLoS ONE*. 2016;11(12):e0167642. doi:10.1371/journal.pone.0167642.

30 Foo VHX, Verkicharla PK, Ikram MK, et al. Axial Length/Corneal Radius of Curvature Ratio and Myopia in 3-Year-Old Children. *Transl Vis Sci Technol*. 2016;5(1):5. doi:10.1167/tvst.5.1.5.

31 Zadnik K, Manny RE, Yu JA, et al. Ocular component data in schoolchildren as a function of age and gender. *Optom Vis Sci*. 2003;80(3):226-236.

32 Hashemi H, Jafarzadehpur E, Ghaderi S, et al. Ocular components during the ages of ocular development. *Acta Ophthalmol*. 2015;93(1):e74-81. doi:10.1111/aos.12498.

33 David A. Atchison, Catherine E. Jones, Katrina L. Schmid, et al. Eye Shape in Emmetropia and Myopia. *Invest. Ophthalmol. Vis. Sci.* 2004;45(10):3380-3386. doi:10.1167/iovs.04-0292.

34 Dr Madhu Sudhan. A COMPARATIVE STUDY IN AXIAL LENGTH OF EYE BETWEEN MYOPES AND EMMETROPES IN INDIAN POPULATION. *International Journal of Evidence-Based Healthcare*. 2015;2(26):3870-3874. https://www.researchgate.net/publication/279205815_A_COMPARATIVE_STUDY_IN_AXIAL_LENGTH_OF_EYE_BETWEEN_MYOPES_AND_EMMETROPES_IN_INDIAN_POPULATION.

35 Kim H-S, Yu D-S, Cho HG, Moon B-Y, Kim S-Y. Comparison of predicted and measured axial length for ophthalmic lens design. *PLoS ONE*. 2019;14(1):e0210387. doi:10.1371/journal.pone.0210387.

36 Tideman JWL, Polling JR, Vingerling JR, et al. Axial length growth and the risk of developing myopia in European children. *Acta Ophthalmol*. 2018;96(3):301-309. doi:10.1111/aos.13603.

37 Huang C-Y, Hou C-H, Lin K-K, Lee J-S, Yang M-L. Relationship of lifestyle and body stature growth with the development of myopia and axial length elongation in Taiwanese elementary school children. *Indian J Ophthalmol*. 2014;62(8):865-869. doi:10.4103/0301-4738.141047.

38 Lu TL, Wu JF, Ye X, et al. Axial Length and Associated Factors in Children: The Shandong Children Eye Study. *Ophthalmologica*. 2016;235(2):78-86. doi:10.1159/000441900.

39 Jin P, Li M, He X, et al. Anterior-Chamber Angle and Axial Length Measurements in Normal Chinese Children. *J Glaucoma*. 2016;25(8):692-697. doi:10.1097/IJG.0000000000000404.

40 Sanz Diez P, Yang L-H, Lu M-X, Wahl S, Ohlendorf A. Growth curves of myopia-related parameters to clinically monitor the refractive development in Chinese schoolchildren. *Graefes Arch Clin Exp Ophthalmol*. 2019. doi:10.1007/s00417-019-04290-6.

41 Poulain T, Baber R, Vogel M, et al. The LIFE Child study: a population-based perinatal and pediatric cohort in Germany. *Eur J Epidemiol*. 2017;32(2):145-158. doi:10.1007/s10654-016-0216-9.

42 Borghi E, Onis M de, Garza C, et al. Construction of the World Health Organization child growth standards: selection of methods for attained growth curves. *Stat Med*. 2006;25(2):247-265. doi:10.1002/sim.2227.

43 Vogel M, Kirsten T, Kratzsch J, Engel C, Kiess W. A combined approach to generate laboratory reference intervals using unbalanced longitudinal data. *J Pediatr Endocrinol Metab*. 2017;30(7):767-773. doi:10.1515/jpem-2017-0171.

44 McCullough SJ, O'Donoghue L, Saunders KJ. Six Year Refractive Change among White Children and Young Adults: Evidence for Significant Increase in Myopia among White UK Children. *PLoS ONE*. 2016;11(1):e0146332. doi:10.1371/journal.pone.0146332.

45 Villarreal MG, Ohlsson J, Abrahamsson M, Sjöstrom A, Sjöstrand J. Myopisation: the refractive tendency in teenagers. Prevalence of myopia among young teenagers in Sweden. *Acta Ophthalmol Scand*. 2000;78(2):177-181. doi:10.1034/j.1600-0420.2000.078002177.x.

46 Lam CS-Y, Lam C-H, Cheng SC-K, Chan LY-L. Prevalence of myopia among Hong Kong Chinese schoolchildren: changes over two decades. *Ophthalmic Physiol Opt*. 2012;32(1):17-24.

47 You QS, Wu LJ, Duan JL, et al. Prevalence of myopia in school children in greater Beijing: the Beijing Childhood Eye Study. *Acta Ophthalmol*. 2014;92(5):e398-406. doi:10.1111/aos.12299.

Appendix

Einreichungserklärung

Medizinische Fakultät der Universität Leipzig

Einreichungserklärung

Die von Carolin Truckenbrod

vorgelegte Dissertation wurde betreut von

Wieland Kiess
und
Christof Meigen

Die Einreichung der Dissertation wird befürwortet.

UNIVERSITÄTSKLINIKUM LEIPZIG AöR
Department für Frauen- und Kindermedizin
Klinik und Poliklinik für Kinder- und Jugendmedizin
Prof. Dr. med. Wieland Kiess
Direktor der Klinik
Liebigstraße 20a, Haus 6 · 04103 Leipzig
Telefon (0341) 97-2 60 00

Leipzig, den 5/5/21

.... Betreuer / Stempel

.... Leiter der Einrichtung/Stempel

.... Ko-Betreuer / Stempel (wenn vorhanden)

.... Leiter der Einrichtung / Stempel (i. F. einer weiteren Einrichtung)

Declaration

Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

27.05.2021

Datum

Unterschrift

Wissenschaftliche Beiträge zu den Publikationen

Contributors statement

Reference curves for refraction in a German cohort of healthy children and adolescents

Carolin Truckenbrod	Conzenptualization, Methodology, Writing, Corresponding author
Christof Meigen	Data analysis, Visualization, Revising the manuscript
Manuela Brandt	Data aquisition, Revising the manuscript
Mandy Vogel	Fundamental work for data analysis, Revising the manuscript
Siegfried Wahl	Supervision
Anne Jurkutat	Revising the manuscript
Wieland Kiess	Project administration

29.4.21

Date Christof Meigen

29.04.21

Date Manuela Brandt

29.04.21

Date Mandy Vogel

29.04.21

Date Siegfried Wahl

29.4.21

Date Anne Jurkutat

5/5/21

Date Wieland Kiess

29.4.21

Date Carolin Truckenbrod

Contributors statement

Impaired visual acuity caused by uncorrected refractive errors and amblyopia in a German paediatric cohort

Manuela Brandt	Conzeptualization, data curation, data analysis, writing
Carolin Truckenbrod	Corresponding author, writing - review and editing
Christof Meigen	Validation, Revising the manuscript
Mandy Vogel	Revising the manuscript
Tanja Poulain	Revising the manuscript
Wieland Kiess	Project administration
Siegfried Wahl	Supervision, Revising the manuscript

Date Manuela Brandt

Date Christof Meigen

Date Mandy Vogel

Date Tanja Poulain

Date Wieland Kiess

Date Siegfried Wahl

Date Carolin Truckenbrod

Contributors statement

Longitudinal analysis of axial length growth in a German cohort of healthy children and adolscents

Carolin Truckenbrod	Conzenptualization, Methodology, Writing, Corresponding author
Christof Meigen	Data analysis, Visualization, Revising the manuscript
Manuela Brandt	Data aquisition, Revising the manuscript
Mandy Vogel	Fundamental work for data analysis, Revising the manuscript
Pablo Sanz Diez	Revising the manuscript
Siegfried Wahl	Supervision, revising the manuscript
Anne Jurkutat	Supervision
Wieland Kiess	Project administration

29.4.21

Date Christof Meigen

29.04.21

Date Manuela Brandt

29.04.21

Date Mandy Vogel

26.04.21

Date Pablo Sanz Diez

29.04.21

Date Siegfried Wahl

29.4.21

Date Anne Jurkutat

5/5/21

Date Wieland Kiess

29.4.21

Date Carolin Truckenbrod

Contributors statement

Refractive status in a German pediatric cohort: A cross-sectional analysis of the LIFE Child data

Manuela Brandt	Conzeptualization, data curation, data analysis, writing
Christof Meigen	Validation, Revising the manuscript
Carolin Truckenbrod	Corresponding author, writing - review and editing
Mandy Vogel	Revising the manuscript
Tanja Poulain	Revising the manuscript
Anne Jurkutat	Supervision
Franziska G. Rauscher	Supervision
Wieland Kiess	Project administration
Siegfried Wahl	Supervision

25.04.21

Date Manuela Brandt

27.4.21

Date Christof Meigen

29.04.21

Date Mandy Vogel

29.4.21

Date Tanja Poulain

29.4.21

Date Anne Jurkutat

Date Franziska G. Rauscher

5/5/21

Date Wieland Kiess

29.04.21

Date Siegfried Wahl

29.4.21

Date Carolin Truckenbrod

Acknowledgments

I want to thank my husband Clemens for his continous support, not only while writing this thesis but in all aspects throughout my studies and my professional carrer. He always organised enough chocolate to keep me going and spent so many hours playing Lego with the children. Also thank you to my children Miriam and Jonas and to my parents, who all made sure, that I have enough spare time for this project.

I am very grateful to the Life child team, who have been a great source of support. Special thanks to the best Co-superviser ever, Christof Meigen, whose guidance and encouragement has been invaluable throughout this study. I also want to thank Mandy Vogel and Tanja Poulain for their support. I want to express my grattitude and appreciation to Prof. Wieland Kiess, who gave me the chance to join the LIFE Child team and to write this thesis.

Finally, I would like to express my thanks to all these wonderful Optometrists who supported my professional career not only as experts and advisors but also as friends: Wolfgang Cagnolati, Thomas Nosch, Simon Barnard, Alex Levit and David Fleischman.