



ORIGINAL ARTICLE

Refractive error magnitude and variability: Relation to age



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KEYWORDS

Age-related refractive error;
Mean ocular refraction;
Refractive error variability;
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Anisometropia

Abstract

Purpose: To investigate mean ocular refraction (MOR) and astigmatism, over the human age range and compare severity of refractive error to earlier studies from clinical populations having large age ranges.

Methods: For this descriptive study patient age, refractive error and history of surgery affecting refraction were abstracted from the Waterloo Eye Study database (WatES). Average MOR, standard deviation of MOR and astigmatism were assessed in relation to age. Refractive distributions for developmental age groups were determined. MOR standard deviation relative to average MOR was evaluated. Data from earlier clinically based studies with similar age ranges were compared to WatES.

Results: Right eye refractive errors were available for 5933 patients with no history of surgery affecting refraction. Average MOR varied with age. Children <1 yr of age were the most hyperopic (+1.79 D) and the highest magnitude of myopia was found at 27yrs (−2.86 D). MOR distributions were leptokurtic, and negatively skewed. The mode varied with age group. MOR variability increased with increasing myopia. Average astigmatism increased gradually to age 60 after which it increased at a faster rate. By 85+ years it was 1.25 D. J_0 power vector became increasingly negative with age. J_{45} power vector values remained close to zero but variability increased at approximately 70 years. In relation to comparable earlier studies, WatES data were most myopic.

Conclusions: Mean ocular refraction and refractive error distribution vary with age. The highest magnitude of myopia is found in young adults. Similar to prevalence, the severity of myopia also appears to have increased since 1931.

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PALABRAS CLAVE

Error refractivo relacionado con la edad;
 Refracción ocular media;
 Variabilidad del error refractivo;
 Astigmatismo;
 Anisometropía

Magnitud y variabilidad del error refractivo: relación con la edad**Resumen**

Objetivo: Estudiar la refracción ocular media (MOR) y el astigmatismo a lo largo del rango de la vida humana, y comparar la magnitud del error refractivo con estudios previos sobre poblaciones clínicas con rangos de edad amplios.

Métodos: Para este estudio descriptivo, se extrajeron de la base de datos Waterloo Eye Study (WatES) la edad del paciente, el error refractivo y el historial de cirugía con repercusión en la refracción. Se evaluaron la MOR media, la desviación estándar de MOR y el astigmatismo con relación a la edad. Se calcularon las distribuciones refractivas para los grupos de edad evolutiva. Se evaluó la desviación estándar de MOR con respecto a MOR media. Se compararon los datos de los estudios clínicos previos con los rangos de edad similares de WatES.

Resultados: Se dispuso de los errores refractivos del ojo derecho de 5.933 pacientes sin historial de cirugía con repercusión en la refracción. La MOR media sufrió variaciones con la edad. Los niños con edad <1 año reflejaron mayor hipermetropía (+1,79D), encontrándose el mayor valor de miopía a los 27 años (-2,86D). Las distribuciones de MOR fueron leptocúrticas, y negativamente sesgadas. La moda varió con el grupo de edad. La variabilidad de MOR se incrementó al aumentar la miopía. El astigmatismo medio aumentó gradualmente hasta los 60 años, pasados los cuales se incrementó a mayor velocidad. A los 85 años, o más, su valor fue de 1,25D. El vector de potencia J_0 se modificó hacia valores más negativos con la edad. Los valores del vector de potencia J_{45} fueron cercanos a 0, aunque su variabilidad se incrementó a los 70 años, aproximadamente. Con relación a los estudios previos comparables, los datos WatES fueron más miópicos.

Conclusiones: La refracción ocular media y la distribución del error refractivo varían con la edad. La mayor magnitud de la miopía se encontró en los adultos jóvenes. Al igual que la prevalencia, la gravedad de la miopía parece haberse incrementado desde 1931.

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Introduction

Refractive error is globally recognized as the leading cause of correctable visual impairment.^{1,2} The high prevalence of significant refractive error and the costs associated with its correction, with spectacles, contact lenses or surgery, pose significant public health and economic concerns.³⁻⁵ However, prevalence is not the only important parameter when evaluating the societal impact of diseases; severity also plays a significant role. It is well known that refractive error related visual impairment increases with increased magnitude of myopia. Higher magnitudes of myopia are much more likely (10–40 times depending on the study) than lower magnitudes to result in sight threatening visual consequences.⁶⁻⁸ Studies investigating the age related prevalence and/or historical change in prevalence of refractive error are quite common. Far fewer studies have looked at what changes occur with age and over generations in the severity of refractive error.

Historically, the literature looking at average refractive errors across a large age-range has been cross-sectional data in clinical populations and indicates that the refractive state of the eye changes with age. In 1931, Tassman⁹ reported on refractive error distributions of hospital patients from newborns through 70+ years of age in ten different age groups. Mean ocular refraction (MOR) was determined from the average of the refractive meridians for each eye. The youngest patients had the highest frequency of hyperopic refractive

errors with narrow distributions. Adult age groups were less hyperopic with broader distributions. Brown¹⁰ (1938) reported shifts in average refraction at one to two year intervals for infant to middle-aged ophthalmic patients. In 1950, Slataper¹¹ reported on “age norms” of refraction of ~18,000 patients ranging in age from birth to 80+ years of age giving average MOR values per year of age. His data showed a steady shift from hyperopia toward myopia from birth until approximately 30 years of age when there was a shift back toward hyperopia with increasing age until age 65, at which time the trend reversed again. Saunders¹² (1981) reported age-related refractive shifts similar to Slataper but with more myopic MOR values overall. Population based surveys and longitudinal studies typically have focused on select age groups such as infants and/or pre-schoolers,¹³⁻¹⁵ school age children,^{16,17} adults,^{3,18-28} and older adults.^{29,30}

Age-dependence for the magnitude and direction of astigmatism has been less thoroughly investigated with the bulk of research considering specific age groups. For example, studies³¹⁻³³ have suggested that infants tend to have a relatively high prevalence of against-the-rule astigmatism (ATR) which shifts to with-the-rule (WTR) by four years of age. The specific age of these transitions varied between studies. Saunders¹² using a cross-sectional design, reported on astigmatism magnitude and direction across the entire human age range. He did not identify any specific trend in the amount of astigmatism with age but found a change in axis from WTR for the youngest age groups to ATR after the

fifth decade. Using J_0 and J_{45} vector representation over the entire human age range Ferrer-Blasco et al.³⁴ showed increasingly negative values to the J_0 cylinder component after 50 years.

The Waterloo Eye Study (WatES) database was developed to study visual and refractive conditions over the entire human age range in a Canadian clinical sample. Previously,³⁵ we reported on the prevalence of refractive error including hyperopia, myopia, astigmatism and anisometropia as a function of age using the WatES database. We also compared myopia prevalence obtained from this database to historical myopia prevalence data, showing increased prevalence over time. Here we report on cross sectional changes in the severity of refractive error; MOR (magnitude and variability) and astigmatism (including J_0 and J_{45} analysis) with age in the same Canadian clinical sample. We now also compare the average magnitude of age-related refractive error for this sample with those obtained from earlier clinically based studies having large age ranges. In this way we identify changes in severity of refractive error over time.

Methods

The WatES database was generated from a retrospective file review of 6397 Paediatric and Primary Care patient visits at the University of Waterloo, School of Optometry and Vision Science clinic during a one year period between January 2007 and January 2008. A complete description of the WatES database including abstraction methods, population representation, data quality analysis, and limitations of the data set has been reported previously.³⁶ Clinical testing at the School of Optometry and Vision Science Clinic is done by third or fourth year optometry interns supervised by licensed optometrists. When results differed between the intern and the supervising optometrist, the optometrist's results were used. The database contains comprehensive information on visual symptoms, ocular and systemic health history, visual function, refractive status, accommodation, binocular vision and ocular health for persons between the age of 0 and 93 years.

Data were extracted by a single experienced optometric practitioner familiar with the clinic files. The abstracted information used in this study included patient age, history of surgery affecting refraction (corneal or lenticular including cataract removal), and refractive error test results (sphere, cylinder and axis if applicable). Race is not identified in the clinic files and therefore was not available for this study. In a sample of data compared to those re-entered by a second abstractor, the disagreement rate for refractive data was low 2–5% depending on the component (Cohen Kappa Statistic $K=0.99$ – 1.00).

In cases where refractive error measurements were not possible or not recorded, individuals were excluded from the analysis. Individuals were also excluded from the main analysis if they had undergone surgery affecting refraction. Refractive error values were taken from balanced subjective refraction, if available (sphere and cylinder in 0.25 D units); otherwise refraction results from monocular testing were used. When subjective refraction testing was not possible, for example in younger children, retinoscopy

results were used. Approximately 3% of the refractions were done using cycloplegia. If refractive error testing was performed after cycloplegia, those values were entered into the database.

Descriptive statistics (mean, standard deviation, mode, kurtosis and skew) were used to characterize the data. Regression analysis was used for determining relationships between two variables. *T*-tests were used to compare mean values between two groups. Individual MOR values were calculated from spherical error plus half the negative cylindrical error. Means and standard deviations of the MOR values were calculated for one year age groups to determine differences in MOR and MOR variability by cross-sectional age bin. For a sub-analysis, this calculation was repeated including values from patients who had undergone surgery affecting refraction to investigate surgical effects on the trend. Patients were then separated into hyperopic, emmetropic and myopic refractive errors based on the same criteria used previously in our prevalence study³⁵ (emmetropia ≥ -0.50 to ≤ 0.50) and average MOR values were plotted against age (1 year age groups) for each refractive error type.

Refractive error distributions were determined by calculating MOR frequency as a percentage of the age group for 0.5 diopter (D) intervals for each of the following age groups: 0–3 years, 4–6 years, 7–19 years, 20–40 years, 41–65 years and 66 years and over. Mode, kurtosis and skewness values were used to characterize the refractive distribution for each of the age groups. Standard deviations of the MOR for each age group (no surgery affecting refraction) were plotted as a function of the average MOR for each age group to determine if there was a relationship between MOR magnitude and MOR variability.

To consider astigmatism as a function of age, the mean cylinder amount was calculated for all individuals of the same age in yearly age groups. All cylinder power and corresponding axis values were also expressed as J_0 and J_{45} , using formulae given by Thibos.³⁷

$$J_0 = \left(-\frac{C}{2}\right) \cos 2\alpha \quad \text{and} \quad J_{45} = \left(-\frac{C}{5}\right) \sin 2\alpha$$

where J_0 is the amount of astigmatism in the horizontal and J_{45} is the amount of astigmatism at 45 degrees. C is the amount of cylinder in the spherocylindrical refraction and α is the axis of the cylinder. Mean J_0 and J_{45} values were then calculated for one year age groups.

Finally, a comparison was made to previous clinic-based studies having large age ranges. Data from the various studies were binned as necessary into 10 year age groups to facilitate comparison.

Results

WatES database patients in this study ranged in age from 2 months to 92 years of age. Right and left eye MOR values for individuals were found to be highly correlated ($r=0.948$) and anisometropia >1 D varied little with age. MOR analyses for right eyes only are reported. There were 6358 patients with refractive error information for the right eye and of those patients 5933 had no history of surgery affecting

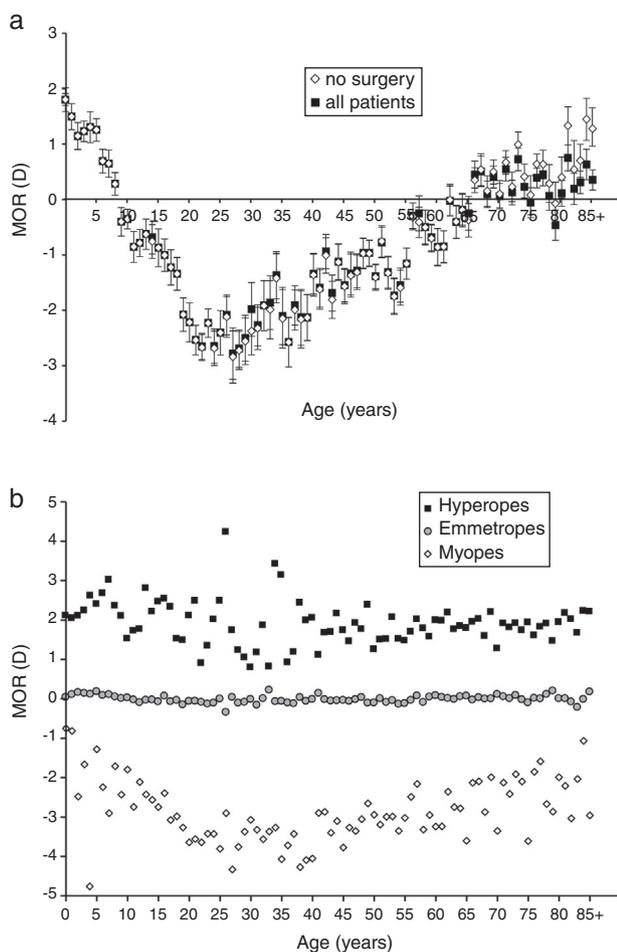


Figure 1 (a) Average MOR (\pm SE) as a function of age for those patients with no surgery and for all patients, (b) average MOR (no surgery) for hyperopes (MOR $>$ 0.50 D), emmetropes (MOR \geq -0.50 D and \leq 0.50 D) and myopes (MOR $<$ -0.50 D) in 1 year age groups (except patients aged 85 years and older who were grouped together).

refraction. Of these, 346 (5.83%) patients were 0–3 years, 320 (5.39%) were 4–6 years, 973 (16.40%) were 7–19 years, 1235 (20.82%) were 20–40 years, 1975 (33.29%) were 41–65 years and 1084 (18.27%) were 66 years of age or older.

Average right eye MOR plotted as a function of yearly age groups is shown in Fig. 1a. The data can be fit well with a bi-linear regression with the inflexion point at 27 years ($y = -0.18x + 1.63$, $r^2 = 0.95$ for $x = 0-27$ and $y = 0.06x - 4.31$, $r^2 = 0.90$ for $x \geq 27$). The most hyperopic average MOR value was +1.79 D in children less than 1 year of age. Subsequently, average MOR values were increasingly more negative resulting in emmetropia by 9 years of age. A minimum average MOR value of -2.86 D was found at 27 years of age after which average MOR values became less myopic until age 66 when they became hyperopic once again. Average MOR, including patients with a history of surgery affecting refraction, is also shown in Fig. 1a. Lenticular surgery for cataract removal accounted for 90% ($n = 382$) of the 425 additional patients included in this data set while corneal refractive surgery accounted for 10% ($n = 43$). The age of occurrence

of minimum MOR was 27 years for both data sets and there was no significant difference in the MOR values between the data sets at this age (t -test $p = 0.93$). Including patients with surgery affecting the refractive state of the eye resulted in significantly less hyperopic MOR values after 65 years of age (t -test $p = 0.01$). When patients are classified with respect to refractive error type it can be seen that the age related patterns in refractive error change are different for the three groups (Fig. 1b). Emmetropes ($N = 1842$) by definition would not change with age, hyperopes ($N = 1682$) initially decrease slightly with age and myopes ($N = 2409$) follow a pattern similar to that shown in Fig. 1a for the sample overall.

MOR distribution changed with age. Fig. 2a–f illustrates the right eye MOR distribution curves for the aforementioned age groups. Table 1 summarizes the descriptive statistics for the MOR distributions from each age group. MOR mode was +1.00 D and +0.50 D for age groups 0–3, and 4–6 years respectively. For all of the remaining age groups, 7–19, 20–40, 41–65 years the mode was 0.00 D except the oldest age group (66+ years), for which the peak frequency occurred at +1.50 D. MOR distribution for age group 0–3 years old was the most leptokurtic while the distribution curve for age group 20–40 years was the least leptokurtic. The distribution for the youngest age group was the most positively skewed (1.57). Skewness became increasingly negative with age and was most negatively skewed for the 66+ years age group (-1.14).

The standard deviation of MOR was plotted as a function of yearly age group in Fig. 3a. Variability in MOR was $>$ 2.00 D in patients between 20 and 50 years of age with a peak standard deviation value of 3.61 D at age 35 years. MOR variability decreased to $<$ 2.00 D for patients older than 50 or younger than 20 years. There is an inverse relationship between average MOR and MOR variability ($y = -0.26x + 2.25$, $r^2 = 0.47$) (Fig. 3b). Standard deviations are lowest for the most positive MOR values and become higher as MOR values become more negative.

Like MOR, the magnitude of right and left eye cylinder for individuals were found to be correlated ($r = 0.723$). When mean cylinder power values for the right eye were plotted against age (Fig. 4a), there was an increase in the average amount of astigmatism with increasing patient age. In patients less than 1 year, the mean amount of astigmatism was approximately 0.50 D. After that, there was a gradual but consistent increase in the amount of astigmatism to 0.80 D in patients aged 60 years. The rate of increase in astigmatism described by $y = 0.44 e^{0.01x}$, $r^2 = 0.68$ was greater after age 60 such that by 85+ years of age, the mean cylinder power was approximately 1.25 D. In addition, when mean J_0 right eye values were plotted in yearly age groups (Fig. 4b), the J_0 power vector, had a slightly positive value at birth but more negative values with increasing age. Fig. 4c demonstrates that both eyes were similar in this trend. When the J_{45} power vector values were plotted in yearly age groups (Fig. 4d & e), values remained close to zero but variability increases at approximately 70 years of age.

Fig. 5 shows the comparison of WatES MOR results to four studies of North American and Western European clinical populations between 1931 and 2003 revealing an overall increase in the severity of myopia over time.^{9,11,12,38}

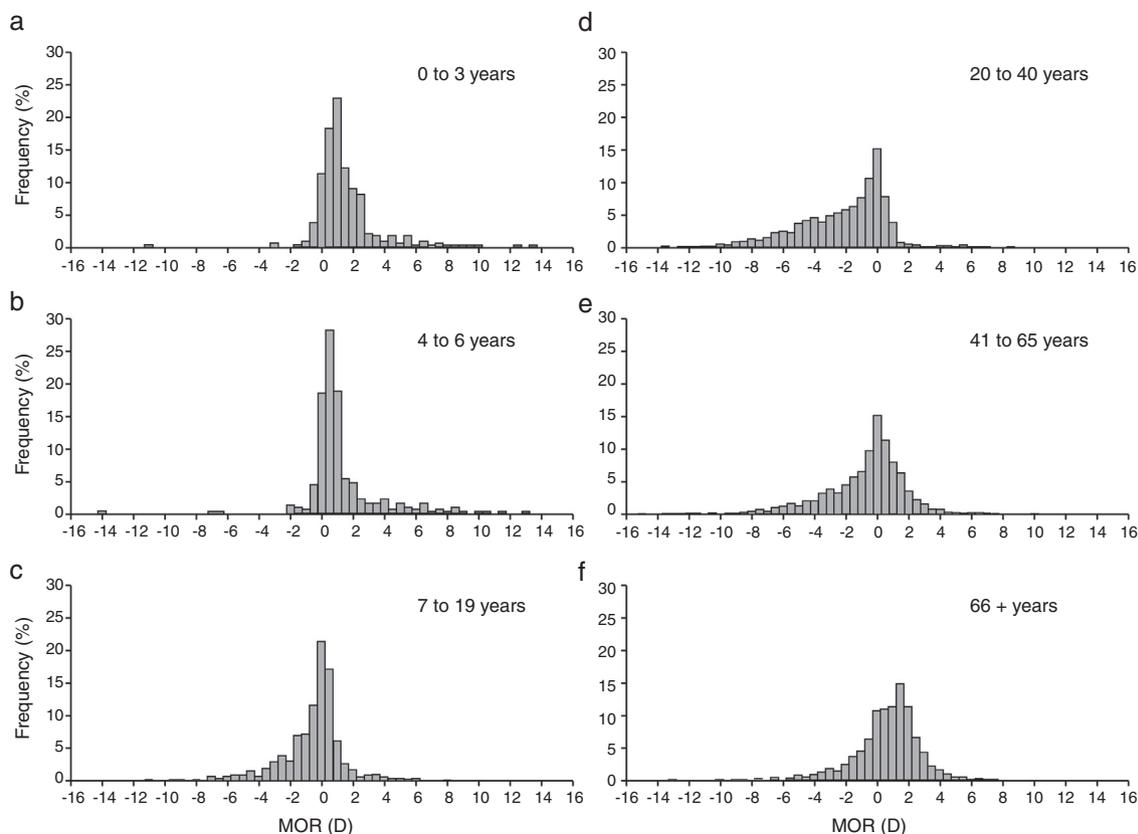


Figure 2 MOR distribution by age group (a) 0–3 yrs, (b) 4–6 yrs, (c) 7–19 yrs, (d) 20–40 yrs, (e) 41–65 yrs, (f) 66+ yrs.

Table 1 Mode, kurtosis, and skewness values for MOR distributions in each age group, in 0.5 D bins.

Age group	Mode	Kurtosis	Skewness
0–3 years	1.0	11.146	1.518
4–6 years	0.5	9.598	0.811
7–19 years	0.0	7.214	−0.680
20–40 years	0.0	0.954	−0.691
41–65 years	0.0	2.572	−0.970
66+ years	1.5	4.017	−1.135

Discussion

Previously we showed the age dependence of refractive error prevalence and increase in myopia prevalence over time in a clinical population.³⁵ Hrynychak et al.³⁵ describes the prevalence of refractive errors for a given criteria e.g., myopia < -0.50 . Prevalence data say little about the severity of myopia. Here, we show the age dependence of refractive error magnitude (severity). The refractive error distributions of the various age groups revealed age-related changes; an important consideration in determining the public health impact of the severity of refractive error as well as for understanding the mechanisms controlling refractive development. MOR values in early childhood were the most leptokurtic and skewed toward hyperopia. Skew became progressively more negative with increasing age groups. Minimum kurtosis occurred in the same age group as

maximum myopic MOR and refractive error variability was greatest when MOR was most myopic. The inverse relationship between MOR variability and MOR has also been shown by Plainis and Charman³⁹ using data from Lin et al.⁴⁰

The data (Figs. 1 and 3) suggest that those individuals who become myopic are in some way fundamentally different than those who do not and that potentially not all myopes are the same. Myopic individuals appear to be responsible for increases in overall refractive error variability and the majority of the overall refractive change that occurs with age. If refractive error were simply a failure of visually guided eye growth the expectation would be that variability increased with the absolute value of refractive error and the signed relationship between variability and MOR would be V-shaped. MOR variability does not increase with increasing hyperopia. It also would be hard to explain the reversal from increasing to decreasing myopic MOR that occurs in the late 20s based on the simple failure of visually guided eye growth.

By comparing to historical studies, we also show an increase in the severity of myopia over time, an important consideration given the visual and disease consequences of high myopia. Direct comparisons between studies are limited by a variety of factors including differences in populations, methods used to collect refractive error data, age groupings and inclusion criteria. The earliest study, Tassman (1931)⁹ used atropine cycloplegia and reported MOR distributions in various age groups of a clinic population in Philadelphia, USA. MOR distribution for his youngest patient group was more positively skewed than in older age groups

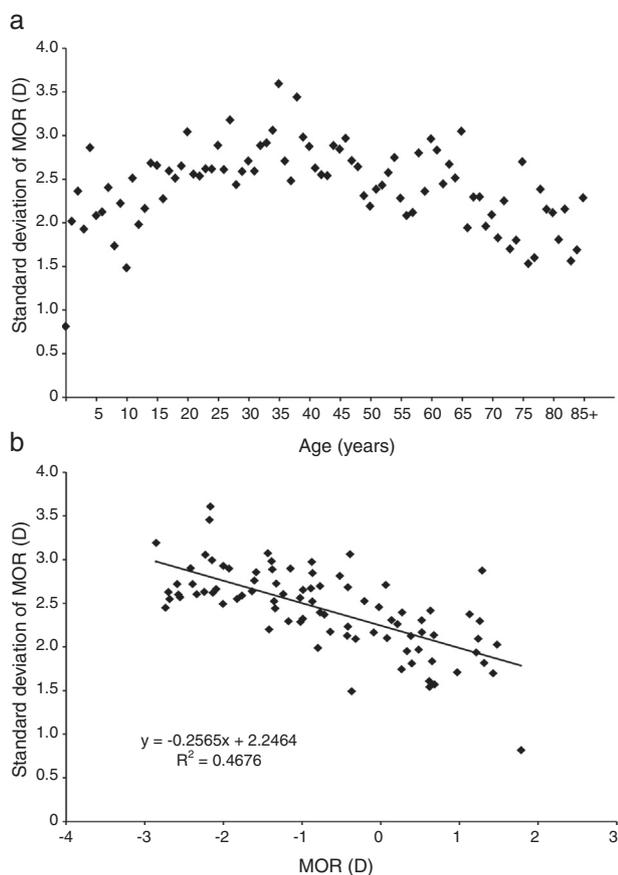


Figure 3 (a) Standard deviation of MOR as a function of age and (b) standard deviation of MOR as a function of average MOR.

similar to the WatES study. However, mean MOR's calculated from these distributions were more hyperopic in all of the age groups than WatES. The data of Slataper (1950)¹¹ are the most hyperopic of the studies, most certainly partly because of the use of several drops of atropine before taking measurements. The 1981 Saunders¹² study from a large optometric clinic population in the United Kingdom is the most similar to WatES; neither used cycloplegia and both used subjective refraction when possible. A comparable amount of hyperopia was reported in early childhood for both studies. However, after that the average MOR was more myopic in the WatES data. The similarity between the two studies in early childhood with increased myopia for older individuals in WatES compared to Saunders suggests that the difference between the two studies is more likely related to environmental than genetic factors. Goldblum et al.³⁸ using data collected by auto-refraction without cycloplegia from 2003 and earlier in Germany, report data very similar to Saunders although slightly more hyperopic in young children.

Unlike the Slataper¹¹ study not every patient in our dataset was refracted under cycloplegia. It was only used when deemed to be clinically necessary. The impact of differences in the use of cycloplegia would be most significant in pre-presbyopic hyperopes. The greatest effect on our study outcome would most probably be to underestimate the rate at which myopic increases occur with age between birth and the late 20s. There also may be an overall myopic shift in those <40 years of age in our study sample but it

is unlikely that this would account for all of the differences seen. It has been shown that even in infants the average difference between cycloplegic and non-cycloplegic refractions is ~ 1 D⁴¹ and our observed differences are larger than this. Lack of cycloplegia should not be responsible at all for the observed overall myopic shift relative to the other studies in persons over 50 years of age.

Changes in the frequency and type of cataract surgery over time^{42,43} would influence MOR values in older adults and may explain some of the differences between the studies. Slataper attributed the dip toward myopia after age 65 to cataract development. Cataract surgery rates were lower in earlier years resulting in more patients with mature cataract, which could skew results in the negative direction. Presumably the lack of a myopic dip in older adults in the Goldblum,³⁸ Saunders¹² and WatES studies reflects the comparatively higher rates of cataract surgery with intraocular lens implants and significantly fewer patients with advanced cataracts in more recent years. Despite the challenges of comparison, the age related trends are fairly similar between studies and there does appear to be an overall shift in the myopic direction across the decades for all ages except the very youngest children. This increase in the severity of myopia is important from a public health perspective as it is likely to be accompanied by an increase in visual impairment.⁶

Because the WatES was a retrospective cross-sectional study, it could be argued that the trends observed in this study were merely due to a cohort effect within the different age groups. There is some evidence that this is not the case. First there is a similarity in the age related pattern of change across studies from various decades. Second, two studies^{30,44} that examined longitudinal vs cohort changes in refractive error also concluded that a true age-related hyperopic shift existed.

Astigmatism in this study also changed with age in a pattern generally consistent with findings from other studies. Unlike WatES and Ferrer-Blasco³⁴ who found an increase of average absolute cylinder value with age, especially in the later years of life, Saunders¹² did not find any meaningful changes in the mean cylinder power. Agreeing with our decrease in J_0 with age, Saunders showed that the prevalence of WTR astigmatism decreased while ATR increased with each decade of life. He also noted that oblique astigmatism increased a small amount after the first decade but stayed relatively constant for the remaining decades of life. In a cross-sectional clinical population age 5–80 years Fledelius and Stubgaard⁴⁵ found corneal astigmatism matched the refractive shift from predominantly WTR in children to more ATR in the oldest patients. Haegerstrom-Portnoy⁴⁶ reported on astigmatism in an older population (59–106 years) using J_0 and J_{45} power vector analysis. From the youngest to the oldest age group, they reported a mean change from -0.02 D to -0.98 D and from -0.01 D to 0.09 D for the primary and oblique vector respectively.

It is important to note that the WatES data comes from a clinic population. A clinic population is likely to have a larger portion of patients who initially visit the clinic with a pre-existing problem and the results cannot be directly extrapolated to the refractive status of the general population. Nonetheless, the trends in our clinic based study are similar to those found in population based

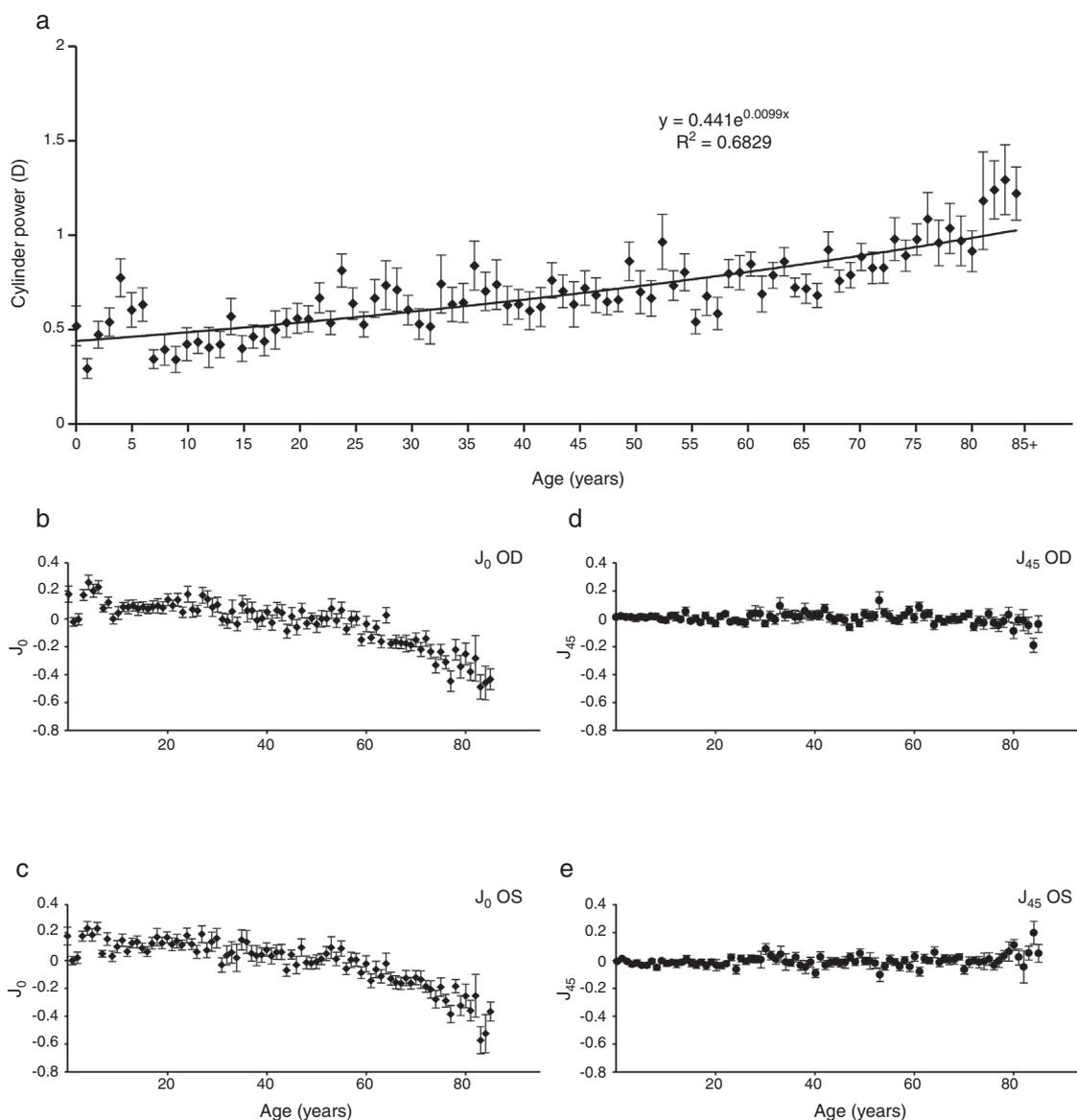


Figure 4 (a) Average positive Cylinder Power (\pm SE) as a function of age and (b–e) average J_0 and J_{45} (\pm SE) for left and right eyes as a function of age. Patients aged 85 years and older are grouped together.

studies although the population based refractive data that are currently available are for specific age groups only. In the Baltimore Pediatric Eye Disease Study,¹³ MOR distributions were skewed to the right with mild hyperopia being the most common condition among infants. There was no statistically significant negative shift in average MOR toward emmetropia from 6 to 72 months of age in that study. Cross-sectional data from the Orinda study found a decrease in average MOR from +0.73 D to +0.50 D between 6 and 12 years of age.⁴⁷ Reports with data on MOR distribution of the adolescent eye are uncommon. One study in Saudi Arabia showed that most children aged 12–13 had a refractive error range between -0.50 D and -3.00 D.⁴⁸ From 1999–2004, the National Health and Nutrition Examination Survey (NHANES) collected refractive error data for anyone age 20 years old and over.⁴⁹ The MOR distributions from NHANES had peak frequencies for refractive errors between -0.50 D and $+0.50$ D

for people aged 20–39 years and 40–59 years while the peak frequency for refractive errors was between $+0.50$ D and $+2.00$ D for people greater than 60 years of age.

In summary, the results of this study show age dependence of refractive error magnitude and variability. At birth, a large portion of infants were hyperopic resulting in hyperopic average MOR values. There was a gradual decrease in average MOR until 27 years of age when average MOR values were the most myopic. Comparing various studies on refractive error conducted since the 1930s suggests that with the exception of infants there has been an overall increase in the magnitude of myopia over the last century. Given the visual and disease consequences of high myopia, this change in severity is a significant finding with public health implications beyond previously documented changes in prevalence. Despite the overall shift the age related trends have remained fairly consistent. Refractive errors

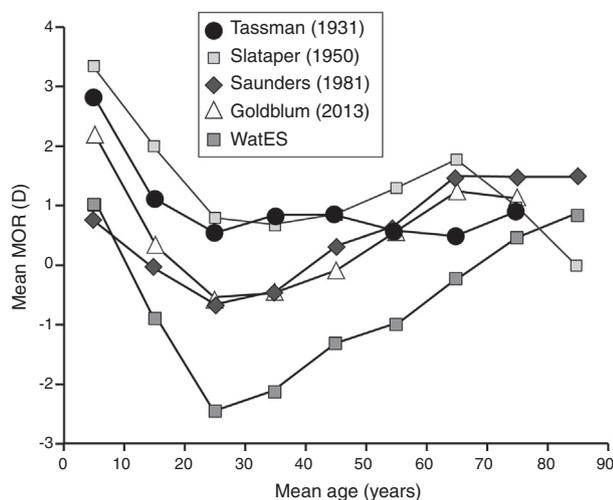


Figure 5 Comparison of the WatES (Canada 2008) mean MOR values as a function of age to other clinically based studies including Tassman⁹ (United States 1931, cycloplegia <40 yrs, aphakia excluded), Slataper¹¹ (United States ~1950, exact dates of data collection not specified, multiple drops of atropine cycloplegia, <-6 D & >+8 D excluded), Saunders¹² (United Kingdom) within 18 month period ~1980) and Goldblum³⁸ (Germany 2003 and earlier, cycloplegia of <14 yrs, autorefraction, based on weighted averages calculated from distribution data) all plotted in 10 year age groups.

were least variable in infancy and there was an inverse relationship between average MOR and MOR variability. Older patients had relatively more ATR astigmatism on average than younger patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

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