Distribution of astigmatism as a function of age in an Australian population

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Distribution of astigmatism as a function of age in an Australian population.

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No conflicts of interest were related to this work.

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Abstract

Purpose: Astigmatism is a common cause of refractive error and is known to vary in prevalence with age. Compared to spherical refractive errors, especially myopia, current efforts to identify genes associated with astigmatism have largely been unrewarding. We aimed to assess the association between refractive astigmatism (RA) and age in order to identify appropriate age cut-offs for maximizing power in genetic studies of astigmatism.

Methods: We performed a cross-sectional analysis of astigmatism data from four Australian-based eye studies comprising 3841 participants aged 5-90 years. In addition to the magnitude and type (against-the-rule [ATR], with-the-rule [WTR], oblique) of RA we calculated the vector components (J0, J45) and evaluated the association of these outcome measures with age.

Results: The magnitude of RA remained relatively stable (mean ± SD [-0.44D ± 0.50]) until individuals reached the age of 50, thereafter increasing in average magnitude by ~1.00 D for those subjects aged 90. The prevalence of clinically significant RA (≥ 1.00D) increased with age and was highest in those aged greater than 70 years (55.1% [47.2 – 62.7%]). Age was significantly associated with RA in adulthood and old age (odds ratio (OR) = 1.04 per one year, p < 0.001).

Conclusions: We have confirmed the previously documented association between RA and age. Our results indicate that most of the observed change occurs after the age of 50, providing a recommended cut-off for participants in genetic studies of this refractive condition.

Keywords: astigmatism, age, epidemiology, genetic disease
Introduction

Uncorrected refractive error is the most common cause of visual impairment worldwide. (Pascolini & Mariotti 2012) Visual morbidity associated with refractive astigmatism (RA) is highly prevalent in some adult populations (Saw et al. 2002; Cheng et al. 2003) and results when the optical system of the eye focuses light as a line instead of a point, requiring cylindrical rather than spherical correction. Consequently, the functional impact of astigmatism on vision may be greater than for other forms of refractive error, whereby altering the accommodative state or viewing distance may mitigate the optical defect. Age and gender, as well as genetic and environmental factors have been shown to influence astigmatism development. Notably, the heritability of astigmatism is high, suggesting a strong genetic etiology of this refractive error. (Sanfilippo et al. 2010)

It is well established that the prevalence of corneal and refractive astigmatism (RA) increases with age, in addition to characteristic changes in the astigmatic axis from with-the-rule (WTR) to against-the-rule (ATR). (Asano et al. 2005; Liu et al. 2011; Leung et al. 2012) Although recent research has identified genes associated with myopia (Wojciechowski 2011; Tang et al. 2014) and spherical refractive error (Stambolian 2013), surprisingly little data has been ascertained for the genetic architecture of RA. As the meta-analysis of large population studies investigating the genetic basis of ophthalmic traits includes individuals of different ages, (Verhoeven et al. 2012) we wished to determine the effect of age on RA.

The primary aim of this study was to evaluate the association between RA and age in a healthy Australian population. In analyzing age associations, we sought to determine the prevalence and characteristics of RA across a wide series of age groups from childhood to older age; thus, providing valuable information about normative data for RA. This
information will play an important role in determining age cut-offs when undertaking analyses of genetic and environmental factors affecting RA.

Materials and Methods

Participants

Participants were identified from four Australian-based studies which examined patients at a similar time point; the Western Australian Pregnancy Cohort (Raine) Study 20-year Eye Follow-Up, the Twins Eye Study Tasmania (TEST), the Norfolk Island Eye Study (NIES), and the Western Australian Eye Protection Study (WAEPS). Participants of the Raine Study had ocular health examinations at the 20-year follow-up of the cohort which was conducted between 2010 – 2012. (McKnight et al. 2012) TEST was established in 2000 to investigate genetic and environmental factors contributing to ocular disease. (Mackey et al. 2009) The NIES commenced in late 2007 in order to determine the prevalence of blindness and ocular conditions that predispose to blindness in the Norfolk Island genetic isolate. (Sherwin et al. 2011) The WAEPS is a community-based study conducted in Perth, Australia to investigate the spectrum of ocular damage and utility eye protection.

The study adhered to the tenets of the Declaration of Helsinki. Ethics approvals have been obtained from the relevant ethics committees of the Royal Victorian Eye and Ear Hospital, University of Tasmania, Griffith University and University of Western Australia. In each cohort, participants provided informed consent at the recruitment stage of the study.

Astigmatism Measurement
All participants had a comprehensive ocular examination that included anterior segment examination, corneal pachymetry, intraocular pressure (IOP) measurement, autorefraction, and a mydriatic optic disc assessment. The same measurement methods and instruments were used in all groups. Autorefracation was performed following cycloplegia in all subjects. In TEST and the NIES, a Humphrey-598 automatic refractor (Carl Zeiss Meditec, Inc., Miami, Florida, USA) was utilised. A Nidek ARK-510A (NIDEK Co. Ltd, Gamagori, Japan) was used in the Raine Study 20-year Eye Follow-up and WAEPS. RA data used in this study are equivalent to the correcting minus cylinder (Cyl) power measured during autorefraction. RA was defined as WTR when the cylinder axis was within 180 ± 30°, ATR when the cylinder axis was within 90 ± 30°, and oblique when otherwise. Clinically significant RA was defined as astigmatism with a Cyl power ≥ 1.00D. Participants with refractive corneal pathology (e.g. keratoconus) or a history of cataract or refractive surgery were excluded from the analysis.

Analyses of RA were conducted including Cyl power as a distinct variable, but also with RA decomposed into its vector components. The power vector approach proposed by Thibos et. al. (Thibos et al. 1997) allows the conversion of Cyl power and axis into constituent vector components incorporating both characteristics of astigmatism, thus enabling a robust statistical approach to its analysis. RA was decomposed into its power vectors by applying a Fourier transformation using the following equations:

\[ \Box_0 = - \frac{C}{2} \times \cos 2\alpha \]

\[ \Box_{45} = - \frac{C}{2} \times \sin 2\alpha \]

where C is negative cylinder power and \( \alpha \) is cylindrical axis. \( \Box_0 \) represents the power vector corresponding to cylinder power set at the 90° and 180° meridians with positive values indicating WTR astigmatism and negative values ATR astigmatism. \( \Box_{45} \) represents
the power vector corresponding to cylinder power set at the 45° and 135° meridians and
reflects oblique astigmatism. Conceptually, it is helpful to interpret vector components in
terms of the Cyl power which is defined as follows:

\[
\text{Cyl power} = 2 \times \sqrt{\theta_0^2 + \theta_{45}^2}
\]

Therefore, if we consider an example where \(\theta_0 = -0.875\) and \(\theta_{45} = 0.00\) in power
vector notation, this equates with 1.75D of Cyl (at 90°) in conventional notation.

Statistical Analysis

Data management and statistical tests were performed in the R statistical environment.(R
Development Core Team) To investigate the effect of age on RA, we divided the total
age range into nine age groups by decades, ranging from 5 - 10 to 81 - 90 years.
Descriptive statistical results for RA by cohort and age group are reported as mean ±
standard deviation (SD). Given that astigmatism data are inherently left-skewed, non-
parametric tests were used to examine differences in RA across gender and age groups
(Wilcoxon rank-sum and Kruskal-Wallis tests). In testing differences in proportions
between youngest and oldest age groups, participants aged 71-90 were analysed as one
group. Multiple logistic regression was conducted to test the associations of age and
gender with clinically significant RA. Two regression models were specified, one with age
as a continuous variable and the other ordered by age group (i.e. age as a categorical
variable). While regression models with continuous predictors are more powerful
statistically than their categorical counterparts, we have also included a categorized age
model to allow direct comparison of age groups for differences in RA. Linear regression
was used to assess the association between RA (Cyl power, \(\theta_0\) and \(\theta_{45}\) vector powers)
and age. As observations from twins are related, non-independence of the data were
addressed in this study by randomly including only one member of each twin pair from
the TEST cohort. Unless otherwise specified all statistical tests were two-sided with a p-value less than 0.05 considered statistically significant.

**Results**

**Distribution of Astigmatism**

Data were available for 3981 subjects. Of these, 140 were ineligible for further assessment due to a history of corneal pathology or corneal/cataract surgery. The remaining 3841 subjects were aged from 5 to 90 years (mean 31 years) and comprised 1821 (47.4%) males and 2020 (52.6%) females. The vast majority of subjects (> 95%) were Caucasian. The differences between right and left eyes for RA were not statistically significant (paired Wilcoxon signed rank test [p = 0.31]) and therefore data from the R eye only were used in subsequent analyses. Demographic and astigmatic data (Cyl, $\square_0$ and $\square_{45}$) stratified by cohort are summarised in Table 1. Overall, RA ranged from 0 to -5.50D with mean and median values of -0.51D and -0.25D, respectively. Figure 1 shows the prevalence of RA (in 0.25D increments) grouped by gender. Notably, the distribution is negatively (left) skewed and as the median RA of -0.25D suggests, at least 50% of the measurements were at this Cyl power or less.

Table 2 summarises astigmatic data in the nine age groups by gender. In general, RA remained relatively stable until the fifth decade of life and then began to increase in magnitude through to the eldest age group. A Bonferroni correction (0.05/11) was performed, with statistical significance defined as $p < 0.005$. Across all groups, the magnitude of Cyl varied significantly with age (Kruskal-Wallis test, $p < 0.001$). In contrast, gender did not have an effect on the magnitude of Cyl in either individual age groups or for the overall cohort.
Characteristics of Astigmatism

The prevalence of RA according to three inclusion criteria based on magnitude and stratified by age group are presented in Table 3. The observed trend across all RA categories was for the prevalence to increase with age. When all magnitudes of RA were considered, the difference in prevalence between youngest (77.8% [95% CI - 70.9 - 83.5%]) and oldest (97.6% [95% CI – 93.6 - 99.2%]) was found to be highly significant (two-proportion Z-test, p < 0.001). Similarly, for RA ≥ 1.00D the prevalence in the youngest and oldest age groups was 8.3% (4.9 – 13.6%) and 55.1% (47.2 – 62.7%) respectively (p < 0.001), compared to 3.3% (1.4 – 7.4%) and 15.6% (10.6 – 22.2%) for RA ≥ 2.00D (p < 0.001).

When categorised by Cyl power, the overall prevalence of RA was 51.9% (95% CI 50.3 – 53.5%) for Cyl <0.50D, 44.8% (43.2 – 46.4%) for Cyl 0.50–1.75D and 3.3% (2.8 – 4.0%) for Cyl >1.75D. As shown in Figure 2(a) the prevalence of Cyl power increased with age. For the lowest magnitude RA category, the proportion of Cyl<0.5D was calculated to be 66.1% in the youngest age group (5 – 10 yrs) compared to 10.8% in the oldest (71 – 90 yrs) (p < 0.001). For Cyl power between 0.5 – 1.75D, prevalences were 30.6% and 73.6% for the youngest and oldest subjects, respectively (two-proportion Z-test, p < 0.001). The difference in prevalence of greater magnitudes of RA (Cyl > 1.75D) was highly significant (3.3% vs 15.6%, p < 0.001).

When the type of RA was considered, ATR astigmatism was most commonly observed, with an overall prevalence of 43.3% [41.5 – 45.0%], compared to WTR (38.8% [95% CI 37.1 – 40.5%]) and oblique (17.9% [16.6 – 19.3%]) forms of RA. Figure 2(b) shows the proportion of each type of RA in the different age groups for all magnitudes of Cyl power. The prevalence of RA type is relatively stable in each age group until the fifth
decade at which time there is a trend towards increasing ATR and decreasing WTR astigmatism into the older age groups. The difference in proportions between youngest and oldest age groups for WTR (37.1% vs 16.6%, p < 0.0001), ATR (42.2% vs 74.8%, p < 0.0001) and oblique RA (20.7% vs 8.6%, p = 0.004) were found to be significant when all Cyl powers were considered.

**Effects of Age and Gender on Astigmatism**

Table 4 shows the results of multiple logistic regression analysis for the effects of age and sex on RA (Cyl ≥ 1.00D) for the two models. When considered as a continuous variable, age was found to positively associated with RA (odds ratio (OR) = 1.04 per one year, p < 0.001). This is equivalent to a 4% increase in the odds of RA with every year increase in age, and a 52% increase in the odds of RA with each decade. The effect of gender in this model was also noted to be significant (p = 0.02) with male gender being positively associated with RA. As we utilized ophthalmic data from four independent population-based studies we included ‘Cohort’ as a covariate in the regression analysis. After adjusting for age and sex, compared to the reference cohort (Raine Study) there was a decrease in the odds of RA (≥1.00D) for subjects from any of the other cohorts. The alternative model we specified allowed age to be categorized and compared with the 5 to 10 year olds (with the exception of those aged 31-40 [p = 0.04]), subjects younger than 50 did not show a greater propensity for astigmatism. In contrast, each of the older age groups (51 – 90 years) demonstrated an increased risk of RA (e.g. [51 – 60 yrs] OR = 3.001, p = 0.001). This effect became greater with successive age groups, such that in subjects aged 81 – 90 there was a 50-fold increase in the odds of having Cyl ≥ 1.00D.

Figure 3 illustrates changes in astigmatism for Cyl, \( \square_0 \) and \( \square_{45} \) vector components for each of the study age groups. The magnitude of RA (Cyl) was relatively stable until
approximately 50 years and then began to increase (corresponding to a decrease in the slope of the lineplot) thereafter. Between the ages of 50 and 90 there was a mean increase in Cyl power of approximately 1.00D. This change was commensurate with the finding from linear regression analysis showing a per 10 year increase in Cyl power of 0.18D (0.15D – 0.22D, [p < 0.001]) after the age of 40 years. Both $\theta_0$ and $\theta_{45}$ vector components remained relatively unchanged until the older age groups where the $\theta_0$ component declined. This reflected a trend towards ATR RA with age; a per 10 year increase in age was associated with a decrease of 0.034D of $\theta_0$ (0.028 – 0.040, [p < 0.0001]). There was no association between the $\theta_{45}$ component and age.

**Discussion**

In this study we evaluated the association between RA and age in several Australian and predominantly urban populations. Four main findings arise from this work; (1) the RA profile remained relatively stable until individuals reached the age of 50; (2) the prevalence of RA increased with age and was highest in those aged greater than 70 years; (3) age was a significant predictor for RA with an increased risk of developing the refractive change into adulthood and old age; (4) a directional shift in the magnitude and type of RA was observed with age such that children tend to have lower magnitudes of WTR RA while adults are inclined to require ATR correcting lenses of higher cylinder power.

Much effort has gone into investigating risk factors for astigmatism with the focus of these on environmental influences on refractive error. The few studies conducted to examine the genetic epidemiology of the disorder have indeed found that environmental factors play a significant role, although not to the exclusion of genetic factors.(Hammond et al. 2001; Grjibovski et al. 2006; Parssinen et al. 2013) Data from the meta-analysis of
genome-wide association studies (GWAS) are now emerging that have identified several putative loci implicated in the development of astigmatism, (Fan et al. 2011; Lopes et al. 2013) but these are not as numerous as those identified for myopia. One possible reason for this is that myopia loci correlate strongly with loci for axial length, whereas the phenotype of RA is more difficult to dissect and involves multiple eye structures, i.e. both the cornea and crystalline lens which may change with age). One of the difficulties that researchers encounter in GWAS methodology is to ensure that the phenotype being examined for genetic association is accurately characterized. If the phenotype is affected by age, selecting for subjects in an age range that the phenotype is known to be stable is an important consideration in study design. In the current context, given that age is associated with RA the same rationale should apply, yet no evidence-based guidelines are available. Rather, studies have simply not considered age as a factor or adopted arbitrary age cut-offs for inclusion in their analyses. Thus, an important finding from this work suggests that utilising data from individuals 50 years and younger may give a more consistent measure of astigmatism providing greater power to identify genetic and environmental factors contributing to the refractive error. Consequently, investigation of change in RA may be a more important variable in individuals over the age of 50 years.

It is clear from these data and from that of other studies that RA is a dynamic component of ocular refraction that, epidemiologically, appears to change with age in a predictable manner. In our study, when all magnitudes of RA were considered the proportion of individuals affected increased from about 78% in children to almost 98% in the oldest age groups. In contrast, when adopting higher magnitudes for defining RA, the proportions of affected individuals decreased but the differences between younger and older age groups was much greater. For individuals aged 71+, more than half (55.1%) were found to have RA ≥ 1.00D with one in six (15.6%) noted to require twice
the amount of astigmatic correction. Our findings are generally consistent with other reports although direct comparisons of prevalence are made more difficult by both differences in definitions (cut-offs) of RA and also diversity of age groups studied. For example, the Blue Mountains Eye Study calculated a prevalence for RA ≥ 0.75D of 37% in subjects aged between 49-97 years. (Attebo et al. 1999) In a comparative East Asian clinical population, Leung et al. determined RA prevalence in a wider age-range of subjects and found that for astigmatism ≥ 1.00D, 41.8% of individuals aged over 60 were affected. (Leung et al. 2012) In contrast, the group found that 17.8% of 3-10 year olds had RA of this magnitude. Considering younger subjects, this is a comparable proportion to that reported in other Asian studies, (Tong et al. 2002; He et al. 2004; Goh et al. 2005) but higher than prevalences calculated in Caucasian cohorts. In a survey of refraction and eye health in over 2200 6-year old Australian school children, the Sydney Myopia Study found a prevalence of 4.8% for RA ≥ 1.00D. (Huynh et al. 2006) While we found a similar proportion of affected 5-10 year olds (8.3%), the Indian experience varies again with a recent study noting only 0.2% of schoolchildren manifested RA of equivalent magnitude. (Padhye et al. 2009) The etiology for such racial differences in prevalence estimates are manifold, but in part may be due to environmental and ethnic factors that vary between populations. For example, Kame et al. suggested that the higher prevalence of RA in some East Asian populations may result from anatomical differences with the propensity for narrower palpebral apertures and ‘tighter’ eyelids in Asians leading to greater rates of astigmatic change. (Kame et al. 1993)

When we examined the prevalence of RA stratified by magnitude and type within each age group (Figure 2), distinct differences in both characteristics were observed between younger and older subjects. Our results reflected an age-trend for RA magnitude with older subjects tending to manifest more Cyl of higher power (> 1.75D) than their
younger counterparts, who conversely, had a higher prevalence of low-powered RA (< 0.5D). The latter finding is in agreement with data from the Sydney Myopia Study (as only children were examined),(Huynh et al. 2006) and although younger subjects were not included, Asano et al. observed the same trend in age-specific prevalences in their cohort of 40–79 year-old Japanese subjects.(Asano et al. 2005) The age-related increase in mean Cyl power found in our study is best visualised in Figure 3 and is consistent with that of the Blue Mountains Eye Study whereby mean Cyl powers of -0.6 D (49–59 years), -0.7 D (60–69 years), -1.0 D (70–79 years) and -1.2 D in persons aged 80–97 years were observed.(Attebo et al. 1999) Leung and colleagues have also previously reported similar changes in median Cyl power with age.(Leung et al. 2012) In terms of outcomes from linear regression analysis, we noted a per 10 year increase in Cyl power of 0.18D and this is comparable to that calculated by Hashemi et al. in an Iranian population of over 5000 40-64 year olds.(Hashemi et al. 2012)

Differences in prevalence of RA type between younger and older subjects were noted for WTR, ATR and oblique forms of astigmatism. Coupled with this, we observed a shift in the axis of RA from WTR in childhood to ATR in older age and this concurs with findings from several studies.(Asano et al. 2005; Guan et al. 2012; Leung et al. 2012; Nemeth et al. 2013) The basis for this shift remains to be fully elucidated although is likely a result of changes in corneal curvature with age.(Baldwin & Mills 1981; Hayashi et al. 1995) Various hypotheses exist to account for the observed trend and involve biomechanical changes intrinsic to the cornea, or occurring as a result of the external anatomy. Age-related remodeling of the cornea may arise from changes in collagen orientation affecting its structural elasticity and rigidity and could reflect the effects of such processes as stromal collagen fibril growth(Daxer et al. 1998) and thickening of Descemet membrane.(Faragher et al. 1997) Extrinsic factors affecting the cornea have
been postulated and include the action of the eyelids and extra-ocular muscles, (Goss 1989; Mori et al. 2002) and intra-ocular pressure on corneal shape. (Duke-Elder 1970)

In our study the observed trend towards ATR astigmatism with age was mirrored in the analysis of cylinder power by its vector components. We found a decrease in the $\theta_0$ component with age ($\sim 0.034$D per 10 years), that is, the value became more negative commensurate with increasing ATR RA. While this effect was in the same direction to that reported in two other recent studies, the size varied almost tenfold. Both in Chinese populations, Guan et. al. found $\theta_0$ decreased by approximately 0.17D with every 10-year increase in age, (Guan et al. 2012) and similarly, Liu et. al. noted a decrease of 0.16D per 10 years of age. (Liu et al. 2011)

To quantify the observational differences in prevalence of RA across the various age categories, age posed a significant risk for developing the refractive disorder. When we considered age a continuous predictor, the OR for RA ($\geq 1.00$D) associated with a per 10-year age increase was determined to be 1.52 (equivalent 5-year age increase 1.23). This represents a similar risk to that calculated by Hashemi et. al. (OR 1.21 per 5 year increase), however, in their analysis RA was defined $\geq 0.50$D. (Hashemi et al. 2012) Leung and colleagues also reported an elevated risk for RA ($\geq 1.00$D), although their regression model was based on age as a categorical predictor. (Leung et al. 2012) Compared to 3 – 10 year olds, subjects aged over 60 years had an almost 3-fold increase in the odds of developing RA of the defined magnitude. In our study, the first age group to differ from the baseline category (5 – 10 years) were those aged 31 – 40 (OR 2.118, $p = 0.04$), although this finding was marginal. Certainly, the odds of RA increased significantly for older subjects, such that those aged 51 – 60 years (OR 3.001, $p = 0.001$) were at greater risk and for those subjects aged 81 – 90 years, the odds were over 50 times higher.
Strengths of the present study include its large population-based sample, the inclusion of subjects with a wide range of ages and the use of cycloplegia to determine refractive status. There are two main limitations of this work with regards to better understanding the potential causal relationship between age and RA. First is the cross-sectional (rather than longitudinal) nature of the study, which does not lend itself to modeling the dynamic processes that influence the outcome of interest. Secondly, we did not investigate the constituent components of RA (i.e. corneal and internal astigmatism) that arise independently and contribute to the total (RA) measured.

In summary, RA is highly prevalent in the elderly Caucasian population in Australia. From lower degrees of WTR astigmatism in children there is a trend towards higher magnitudes of ATR RA in adults and especially the elderly. However the majority of this change tends to occur after the age of 50 with subjects demonstrating a relatively stable RA profile into their 40’s. Our findings describing the distribution and characteristics of RA in this cohort add to the existing literature on astigmatic refractive error and its development. More work needs to be done in fully dissecting the relationship between RA and age and this will likely emerge from longitudinal analyses. In the meantime these data serve as a useful resource for determining an appropriate age range to study in investigations aiming to identify genetic causes of astigmatism.
Acknowledgements

We are grateful to all the study participants. We thank the research staff for cohort coordination and data collection.
References


**Legends**

Figure 1: Histogram showing the distribution of Cyl (truncated at -3.75D) for males and females (across all cohorts).

Figure 2(a): Prevalence of refractive astigmatism magnitude by age group.

Figure 2(b): Prevalence of astigmatism type by age group (for all RA).

Figure 3: Mean values of Cyl, J0, and J45 astigmatic components as a function of age for refractive astigmatism. The upper and lower error bars represent standard errors of the mean.

Table 1: Demographic information and Cyl magnitude (vector components, J0 and J45) for the four cohorts in the study.

Table 2: Demographic information and Cyl magnitude (vector components, J0 and J45) for the nine age groups.

Table 3: Prevalence (95% CI) of RA in the nine age groups.

Table 4: Multiple logistic regression of age, sex and cohort on Cyl (≥1.00D). Two analyses are presented – one with age as a continuous variable* and one with age categorized by decade†. (Significant results in bold)
Age Group | Prevalence | Cyl Power
---|---|---
5−10 |  | 
11−20 |  | 
21−30 |  | 
31−40 |  | 
41−50 |  | 
51−60 |  | 
61−70 |  | 
71−80 |  | 
81−90 |  | 

Cyl Power:
- <0.5D
- 0.5−1.75D
- >1.75D
Table 1: Demographic information and Cyl magnitude (vector components, J0 and J45) for the four cohorts in the study.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Gender</th>
<th>n</th>
<th>Age (Mean - Range)</th>
<th>Cyl (Mean ± SD)</th>
<th>J0 (Mean ± SD)</th>
<th>J45 (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raine</td>
<td>M</td>
<td>682</td>
<td>20 (19-22)</td>
<td>-0.53±0.55</td>
<td>0.01±0.35</td>
<td>-0.02±0.20</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>642</td>
<td>20 (18-22)</td>
<td>-0.46±0.42</td>
<td>0.03±0.29</td>
<td>-0.03±0.15</td>
</tr>
<tr>
<td>Test</td>
<td>M</td>
<td>552</td>
<td>21 (5-90)</td>
<td>-0.37±0.51</td>
<td>-0.02±0.34</td>
<td>-0.01±0.18</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>679</td>
<td>23 (5-83)</td>
<td>-0.40±0.53</td>
<td>0.00±0.33</td>
<td>0.00±0.23</td>
</tr>
<tr>
<td>Nies</td>
<td>M</td>
<td>327</td>
<td>51 (7-89)</td>
<td>-0.67±0.73</td>
<td>-0.08±0.45</td>
<td>-0.02±0.26</td>
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<tr>
<td></td>
<td>F</td>
<td>397</td>
<td>50 (9-89)</td>
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<td>-0.01±0.34</td>
<td>0.01±0.23</td>
</tr>
<tr>
<td>Eps</td>
<td>M</td>
<td>260</td>
<td>53 (16-83)</td>
<td>-0.80±0.73</td>
<td>-0.19±0.46</td>
<td>0.02±0.24</td>
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<tr>
<td></td>
<td>F</td>
<td>302</td>
<td>52 (10-89)</td>
<td>-0.70±0.57</td>
<td>-0.12±0.40</td>
<td>0.00±0.22</td>
</tr>
<tr>
<td>Overall</td>
<td>M</td>
<td>1821</td>
<td>30 (5-90)</td>
<td>-0.54±0.62</td>
<td>-0.05±0.39</td>
<td>-0.01±0.22</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>2020</td>
<td>32 (5-89)</td>
<td>-0.49±0.52</td>
<td>-0.01±0.33</td>
<td>-0.01±0.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3841</td>
<td>31 (5-90)</td>
<td>-0.51±0.57</td>
<td>-0.03±0.36</td>
<td>-0.01±0.21</td>
</tr>
</tbody>
</table>
Table 2: Demographic information and Cyl magnitude (vector components, J0 and J45) for the nine age groups.

<table>
<thead>
<tr>
<th>Age Group (yrs)</th>
<th>Gender</th>
<th>n</th>
<th>Cyl (Mean ± SD)</th>
<th>J0 (Mean ± SD)</th>
<th>J45 (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - 10</td>
<td>M</td>
<td>94</td>
<td>-0.41±0.72</td>
<td>0.09±0.43</td>
<td>0.03±0.14</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>86</td>
<td>-0.48±0.70</td>
<td>-0.01±0.37</td>
<td>0.06±0.30</td>
</tr>
<tr>
<td>11 - 20</td>
<td>M</td>
<td>843</td>
<td>-0.46±0.49</td>
<td>-0.01±0.32</td>
<td>-0.02±0.18</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>868</td>
<td>-0.41±0.42</td>
<td>0.01±0.28</td>
<td>-0.02±0.15</td>
</tr>
<tr>
<td>21 - 30</td>
<td>M</td>
<td>327</td>
<td>-0.44±0.56</td>
<td>0.01±0.35</td>
<td>-0.03±0.22</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>354</td>
<td>-0.41±0.49</td>
<td>0.05±0.32</td>
<td>-0.02±0.19</td>
</tr>
<tr>
<td>31 - 40</td>
<td>M</td>
<td>85</td>
<td>-0.53±0.65</td>
<td>0.01±0.39</td>
<td>0.03±0.26</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>113</td>
<td>-0.46±0.50</td>
<td>0.03±0.29</td>
<td>0.05±0.24</td>
</tr>
<tr>
<td>41 - 50</td>
<td>M</td>
<td>108</td>
<td>-0.58±0.51</td>
<td>-0.05±0.33</td>
<td>0.00±0.22</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>180</td>
<td>-0.47±0.47</td>
<td>-0.04±0.30</td>
<td>0.03±0.20</td>
</tr>
<tr>
<td>51 - 60</td>
<td>M</td>
<td>147</td>
<td>-0.74±0.83</td>
<td>-0.11±0.52</td>
<td>-0.03±0.24</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>186</td>
<td>-0.56±0.47</td>
<td>-0.01±0.31</td>
<td>0.02±0.23</td>
</tr>
<tr>
<td>61 - 70</td>
<td>M</td>
<td>130</td>
<td>-0.73±0.63</td>
<td>-0.18±0.39</td>
<td>0.03±0.25</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>153</td>
<td>-0.77±0.64</td>
<td>-0.05±0.44</td>
<td>0.00±0.26</td>
</tr>
<tr>
<td>71 - 80</td>
<td>M</td>
<td>75</td>
<td>-1.13±0.80</td>
<td>-0.35±0.56</td>
<td>0.00±0.24</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>70</td>
<td>-1.05±0.78</td>
<td>-0.22±0.55</td>
<td>-0.06±0.29</td>
</tr>
<tr>
<td>81 - 90</td>
<td>M</td>
<td>12</td>
<td>-1.88±1.11</td>
<td>-0.58±0.60</td>
<td>-0.24±0.69</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>10</td>
<td>-1.08±0.57</td>
<td>-0.33±0.50</td>
<td>-0.04±0.28</td>
</tr>
</tbody>
</table>
Table 3: Prevalence (95% CI) of RA in the nine age groups.

<table>
<thead>
<tr>
<th>Age Group (yrs)</th>
<th>n</th>
<th>Prevalence % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Cyl ≥ 0.25D</strong></td>
</tr>
<tr>
<td>5 – 10</td>
<td>180</td>
<td>77.8 (70.9 – 83.5)</td>
</tr>
<tr>
<td>11 – 20</td>
<td>1711</td>
<td>82.3 (80.4 – 84.1)</td>
</tr>
<tr>
<td>21 – 30</td>
<td>681</td>
<td>73.0 (69.4 – 76.3)</td>
</tr>
<tr>
<td>31 – 40</td>
<td>198</td>
<td>79.3 (72.8 – 84.6)</td>
</tr>
<tr>
<td>41 – 50</td>
<td>288</td>
<td>86.5 (81.8 – 90.1)</td>
</tr>
<tr>
<td>51 – 60</td>
<td>333</td>
<td>91.9 (88.3 – 94.5)</td>
</tr>
<tr>
<td>61 – 70</td>
<td>283</td>
<td>94.0 (90.4 – 96.4)</td>
</tr>
<tr>
<td>71 – 80</td>
<td>145</td>
<td>97.9 (93.6 – 99.5)</td>
</tr>
<tr>
<td>81 – 90</td>
<td>22</td>
<td>95.5 (75.1 – 99.8)</td>
</tr>
</tbody>
</table>
Table 4: Multiple logistic regression of age, sex and cohort on Cyl (≥1.00D). Two analyses are presented – one with age as a continuous variable* and one with age categorized by decade†. (Significant results in bold)

<table>
<thead>
<tr>
<th>Variables</th>
<th>B coefficient (95% CI)</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-2.901 (-3.147 - -2.661)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (continuous)*</td>
<td>0.043 (0.035 – 0.050)</td>
<td>1.043 (1.036 – 1.051)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>M 0.217 (0.035 – 0.401)</td>
<td>1.243 (1.036 – 1.493)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cohort</td>
<td>EPS -0.495 (-0.874 - -0.124)</td>
<td>0.609 (0.417 – 0.883)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>NIES -0.850 (-1.219 - -0.490)</td>
<td>0.427 (0.295 – 0.613)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>TEST -0.458 (-0.717 - -0.202)</td>
<td>0.633 (0.488 – 0.817)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

| Intercept  | -2.322 (-3.004 - -1.694)        |                  | <0.0001|
| Age Group† | 11 - 20 -0.133 (-0.702 - -0.496) | 0.876 (0.495 – 1.642) | 0.66   |
|            | 21 - 30 0.191 (-0.374 – 0.816)  | 1.210 (0.688 – 2.261) | 0.53   |
|            | 31 - 40 0.750 (0.065 – 1.469)   | 2.118 (1.068 – 4.343) | 0.04   |
|            | 41 - 50 0.602 (-0.057 – 1.301)  | 1.826 (0.945 – 3.674) | 0.08   |
|            | 51 - 60 1.099 (0.454 – 1.792)   | 3.001 (1.574 – 5.999) | 0.001  |
|            | 61 - 70 1.594 (0.949 – 2.287)   | 4.923 (2.583 – 9.849) | <0.0001|
|            | 71 - 80 2.417 (1.736 – 3.144)   | 11.218 (5.675 – 23.205) | <0.0001|
|            | 81 - 90 3.930 (2.767 – 5.304)   | 50.899 (15.904 – 201.201) | <0.0001|
| Sex        | M 0.189 (0.005 – 0.373)         | 1.208 (1.005 – 1.453) | 0.04   |
| Cohort     | EPS -0.375 (-0.814 – 0.054)     | 0.687 (0.443 – 1.055) | 0.09   |
|            | NIES -0.707 (-1.145 - -0.279)   | 0.493 (0.318 – 0.756) | 0.001  |
|            | TEST -0.549 (-0.850 - -0.226)   | 0.577 (0.427 – 0.774) | 0.0003 |