Evidence for a Relative Thinning of the Peripheral Cornea with Age in White European Subjects

Sven Jonuscheit and Michael J. Doughty

**PURPOSE.** To investigate age-related differences in central and peripheral corneal thickness in humans with univariate and multivariate regression analyses.

**METHODS.** Orbscan II (Bausch & Lomb, Inc., Rochester, NY) pachymetry was used to assess the cornea in healthy, white European subjects. A corneal thickness profile across an 8-mm chord along the horizontal meridian was generated at 0.5-mm intervals. Univariate and multivariate regression analyses were used to assess any predictable age-related differences, especially in the peripheral cornea.

**RESULTS.** One hundred nine subjects (109 eyes), aged 18 to 82 years with a mean central corneal thickness (CCT) of 0.585 ± 0.040 mm (± SD, no acoustic factor applied) showed no age-related differences of CCT ($P = 0.381$). Regression analyses indicated no substantial age-related differences at any location except at 4 mm from center on the nasal side ($P = 0.036$). However, if considered in relative terms as the corneal thickness profile index (CTPI), a just-significant, age-related, relative thinning was detected at 2.5 mm from center ($P = 0.027$, nasal). The thinning was even more notable at 3 mm ($P < 0.001$, $r = −0.322$) and was substantial at 4 mm ($P < 0.001$, $r = −0.505$). Multivariate regression analysis supported these results and indicated that CTPI was best predicted by a combination of age and posterior corneal curvature.

**CONCLUSIONS.** The results of this study provide evidence that comparing relative thicknesses emphasizes any age-related pachymetry differences and confirmed substantial age-related thinning of the peripheral cornea in healthy white European individuals. These findings should be considered in assessments of refractive surgery patients. (Invest Ophthalmol Vis Sci. 2009;50:4121–4128) DOI:10.1167/iovs.08-3298

Early optical pachymetry studies indicated the central cornea could normally have a thickness of anywhere between 0.46 and 0.67 mm.1 This conclusion was later extended and refined by a review of 230 pachymetry studies published between 1968 and 1999, providing an estimate of the 95% confidence interval for central corneal thickness (CCT) in normal non-Oriental eyes as 0.473 to 0.595 mm.2 Although most studies indicate that CCT should change substantially in infancy and very early childhood,3 little or no further change is expected over the adult years in white (Caucasian) individuals.2

Most pachymetry studies have been limited to CCT assessments, but some have been made of corneal thickness outside the central optical zone by both optical and ultrasound-based methods. These studies have indicated that the cornea gets progressively thicker toward the periphery in most people.2 However, with differences between the locations at which more peripheral measurements have been made, the nature of any age-related changes in peripheral corneal thickness remains rather unclear. In addition, very few research groups have even attempted to report measurements taken close to the true periphery of the cornea (i.e., close to the limbus), let alone to assess whether there are any age-related differences. There are two notable exceptions: a slit lamp-based study indicating that the peripheral corneal thickness could be the same or even slightly less than central corneal thickness measures4 and a later ultrasound pachymetry study indicating a similar, but not quite as extensive, age-related reduction in peripheral corneal thicknesses.5 In white (Caucasian) individuals, with no significant change in CCT, this would indicate an age-related thinning of the peripheral cornea.

As reviewed in detail elsewhere,7 corneal thickness can be measured with a variety of instruments including optical pachymetry, specular microscope, and ultrasound-based pachymeters. Newer instruments include the scanning slit optical method incorporated in the Orbscan II (Bausch & Lomb, Inc., Rochester, NY),6 which allows clinicians and researchers to generate multifaceted corneal outputs such as corneal power maps and global pachymetry and elevation charts.7 These can also be used to generate a profile of the corneal thickness along any particular meridian of the cornea, as the proprietary software provides a set of corneal thickness measures based on the spatial difference between the anterior and the posterior corneal reflections.8,9 Other recent studies that considered age have compared thicknesses averaged over 2-mm diameter zones in the mid-peripheral cornea6 or have used the Orbscan global pachymetry maps to manually extract corneal thickness data to generate discrete sets of thickness data at discrete (0.5 mm) intervals across the horizontal meridian of the cornea, especially over an 8-mm wide chord.9 Similar procedures can be undertaken with both the rotary scanning procedures used in a rotary scanning system (Pentacam; Oculus, Lynnwood, WA),10 and also with optical coherence tomography methods where the eye is turned to different locations to record corneal thickness.11 This type of approach to using Orbscan pachymetry maps allows in theory for detailed analyses to be undertaken of any age-related differences in thickness at any particular location across the cornea. In practice, the most complete and reliable set of Orbscan data are more likely to be obtained along the horizontal meridian of the cornea.9 Similar strategies have been used in other pachymetry studies, and allow also for consideration of the corneal thickness profile in relation to the horizontal corneal diameter (HCD). The goal of the present study was to undertake a detailed analysis of corneal maps to assess the location at which any age-related differences of the more peripheral cornea might be evident, as well as to determine what other factors might determine such

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From the Department of Vision Sciences, Glasgow Caledonian University, Glasgow, Scotland, United Kingdom.

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Corresponding author: Sven Jonuscheit, Department of Vision Sciences, Glasgow Caledonian University, Cowcaddens Road, Glasgow, G4 0BA, Scotland, UK; sven.jonuscheit@gcal.ac.uk.
an age-related thinning. The horizontal meridian of the cornea was selected such that the corneal thickness profile could be specifically assessed with respect to HCD.

**Materials and Methods**

**Subjects**

A cohort of normal individuals of white European origin living in the greater Glasgow area (Scotland) was recruited. The study protocol and all procedures described in this article adhered to the tenets of the Declaration of Helsinki and were approved by the institution’s ethics committee. Written informed consent was obtained from all subjects before enrollment. Exclusion criteria were any form of previous ocular surgery or history of significant ocular disease, and astigmatism > 2.00 D. Previous or current contact lens wear was not used as exclusion criteria, especially since no statistically significant difference in the relative central and mid-peripheral thicknesses has been noted in other contact lens studies. A wide range of ages was included to allow for quantitative analysis of any age-dependent differences of the corneal thickness profile.

**Clinical Assessments**

All subjects underwent a routine examination of the anterior segment. All noncontact measurements were obtained first, and after topical anesthetic was instilled, contact procedures were performed. Assessments included testing Snellen visual acuity, slit lamp biomicroscopy, external eye appearance with digital photography, noncontact specular microscopy of the central region of the endothelium (model SP-2000P; Topcon Corp., Tokyo, Japan) and nonmydriatic fundus photography (model NW65; Topcon; equipped with D1X; Nikon UK Ltd., Kingston-on-Thames, UK). For this study, scanning slit topography (Orbscan II, ver. 2.1; Bausch & Lomb Inc.) was used to acquire three acceptable scans from right eyes. The subjects were asked to position themselves and blink a couple of times before each scan. The quality of the scans was critically reviewed to ensure that adequate detail was available across the horizontal meridian of the cornea, and in most subjects this was achieved with three successive scans taken over a few minutes. In the remaining few subjects, a fourth acquisition was required. As detailed elsewhere on other groups of subjects, including contact lens wearers, the repeat scans are highly reproducible with no detectable differences between the three scans. From the pachymetry data output mode, single-point thickness measurements from 17 locations (eight temporal and eight nasal locations as well as from the central point of the cornea), nominally 0.5 mm apart, were manually extracted. No correction factor was applied to the pachymetry measurements. Data for the anterior and posterior radii of corneal curvature, HCD (white-to-white) and anterior chamber depth (ACD) measures were also extracted. In all cases, averages were calculated from the three scans.

Relative Peripheral Corneal Thickness

For each corneal thickness measured in more peripheral locations, its magnitude relative to central corneal thickness was calculated. The result is referred to as the corneal thickness profile index (CTPI) and is expressed as the ratio between the respective peripheral thickness and the central point thickness. The CTPI is similar in principle to the keratoconus index calculated from either topography data or pachymetry data, except that in the present study it was systematically applied in a stepwise fashion to all 16 discrete data points along the horizontal meridian of the cornea (excluding the center).

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### Statistical Analysis

All data were entered into spreadsheets (SPSS ver. 11 for Apple Macintosh [Cupertino, CA]; SPSS Inc, Chicago, IL) to calculate averages and group mean ± SD, and to generate graphics. Normality of the data sets was tested with the Kolmogorov-Smirnov test and appropriate parametric or nonparametric tests were then used to assess any differences between pachymetry measures at the various corneal locations. Univariate regression was then performed, followed by multivariate regression analyses. Criteria for the entry of independent variables were defined before data entry began, and these criteria were not refined during the analyses. First, univariate linear regression analysis with Pearson’s correlation coefficient (r) was used to assess age-related differences in thickness or CTPI data, as well as any predictable association of both absolute corneal thickness and CTPI with posterior radius of corneal curvature, HCD, and axial length as independent variables. After the univariate regression analyses, a stepwise multivariate regression model was generated, into which the previously used independent variables were entered in descending order, starting with the variable that had the greatest effect on corneal thickness (i.e., the highest r) in the univariate analyses, followed by the second, third, and fourth highest r. Factors that showed no significant association to corneal thickness were not included in the multivariate model. Partial correlation coefficients were determined to define any interrelationship between CTPI and a particular independent factor while controlling for the other independent variables in the model.

### Results

Sets of pachymetry data were initially obtained from 121 adult subjects, aged 18 to 82 years. These subjects all met the criteria of having no history of any significant ocular disease or any form of ocular surgery. In subsequent analyses, 12 subjects were identified with abnormal appearance of the corneal endothelium, and/or abnormalities of the fundus considered to be outside normal limits and were therefore excluded. Corneal endothelial abnormalities were principally those where there was a substantial presence of guttata or pseudoguttata. Fundus abnormalities that warranted exclusion included any notable peripapillary atrophy or evidence of a tilted disc, both of which were more likely associated with higher degrees of myopia. Ultimately, 109 subjects were included in the analyses. The mean age of these subjects was 43 ± 16 years, their mean spherical equivalent refractive error was −2.22 D, with a mean axial length of 24.18 mm. Twenty-four had a history of some form of contact lens wear.

Figure 1 shows a representative set of pachymetry map outputs (Orbscan II; Bausch & Lomb, Inc.) and their equivalent sets of data extracted for the thickness profile across the horizontal meridian. All three scans were considered usable, all showing a well-defined, thinner central zone from which there was a smooth and progressive increase in thickness in all meridians. The apex is slightly lower than the horizontal meridian, a consistent feature in the three separate scans with the subject blinking and refocusing between each scan (Figs. 1A–C). The sets of pachymetry data (Figs. 1D–F) showed the outputs to be very similar but not identical, especially with respect to the greatest thicknesses. The extreme nasal (4 mm off-center) thickness was slightly higher than the temporal thickness (0.706 mm vs. 0.692 mm; Fig. 1D). In the second scan, this nasal versus temporal difference was slightly greater (0.705 mm vs. 0.683 mm, Fig. 1E), whereas in the third scan (Fig. 1F) the extreme nasal and temporal measures were the same (0.692 mm vs. 0.693 mm).

When data from the three scans from this subject were averaged, the central point thickness was 0.577 mm, the nasal (4 mm point) thickness was 0.702 mm, and the temporal 4-mm thickness was 0.660 mm. All data sets were averaged to yield...
group mean thicknesses for the center and the temporal and nasal periphery.

The averaged thickness data from each scan (e.g., Figs. 1D–F) were then used to calculate the relative thickness increase from the center point to each peripheral location, thereby generating the CTPI profile (Figs. 2A–C). The mean central point thickness \( \pm \) SD was 0.585 \( \pm \) 0.040 mm, which was 1.00 on the y-axis (equaling 100%) for the CTPI calculations. The mean nasal CTPI at 4 mm was 1.21 (i.e., the cornea at this location was 21% thicker than at the center), whereas that at the temporal aspect was 1.19 (i.e., the location was 19% thicker than the center), a measurement that was statistically thinner than that calculated 4 mm nasally \((P < 0.001)\). The range of CTPIs got progressively larger from the center with the range at the 4-mm location being 1.01 to 1.34, all corneas being slightly thicker at the most peripheral locations, but with some mid-peripheral measures being only marginally different from that at the central point location.

**Determinants of Central and Peripheral Corneal Thickness: Univariate Analyses**

Univariate linear regression analysis showed no predictable relationship between central corneal thickness and age \((P = 0.381, r = 0.085, \text{Fig. 3A})\). The same regression analyses were repeated at each data location point (i.e., at 0.5 mm from...
center nasal and temporal, 1 mm from center nasal and temporal, and so forth). No age-dependent difference in absolute thicknesses was detected until 4 mm either side of center \( (P \geq 0.141) \). At the 4-mm temporal location, a slight trend was noted (i.e., the absolute thicknesses were slightly lower in older individuals, but not significantly \( (P = 0.141) \). At the 4-mm nasal location (Fig. 3C), the trend was just statistically significant \( (P = 0.036, r = -0.217) \). Removing the 82-year-old subject from the data set did not change the results of the univariate regression analysis substantially. Absolute central \( (P = 0.278) \) and peripheral corneal thickness \( (P \geq 0.191) \) were unrelated to age. Most other univariate regressions also revealed no detectable change in central point thicknesses with respect to anterior corneal curvature, posterior corneal curvature, axial length, or refractive error \( (P \geq 0.482) \).

However, analysis of relative (normalized) corneal thickness CTPI data revealed substantial age-related differences starting in the mid-periphery (Fig. 4). At the 2.5 mm temporal location, there was no age-dependent difference in the relative thickness \( (P = 0.350, \text{Fig. 4A}) \), but there was a just detectable difference on the nasal side \( (P = 0.027, \text{Fig. 4B}) \). At 3 mm from the central point, there was an obvious negative slope to the age-related regression analysis plots (Figs. 4C, 4D), and the difference on the nasal side was statistically significant \( (P < 0.001, r = -0.322) \). A more notable effect was seen for the 3.5-mm data \( (P < 0.001, r = -0.451) \), and even more pronounced at 4 mm (Figs. 4E, 4F). The correlation coefficients \( (r) \) were \(-0.362\) temporally and \(-0.505\) nasally. Exclusion of the data from the 82-year-old subject revealed that CTPIs were still dependent on age and the effect was still more pronounced nasally \( (P < 0.001, r = -0.448) \) than temporally \( (P < 0.001, r = -0.542) \). The coefficients of correlation were slightly lower than those with the inclusion of the 82-year-old's data.

Age was clearly a reasonable predictor of the difference between peripheral corneal thickness (4 mm from center) and CCT, with progressively lower CTPIs with increasing age (Fig. 4, \( r = -0.505 \) nasal, \( r = -0.362 \) temporally). Other anatomic aspects of the cornea and the eye, however, can be shown to contribute to the age-related relative difference in thicknesses (Table 1). Overall, lower CTPIs tended to be seen in corneas with greater posterior radii (i.e., less curved or flatter posterior surface; \( P < 0.001 \)), but posterior radius was a slightly less strong predictor of CTPI than age. Similarly, lower CTPIs were more likely to be seen in corneas with a larger diameter, as assessed by HCD measures on Orbscan \( (P \leq 0.002) \), but the associations were weaker than those seen for age or posterior radius. As another dimensional attribute of the eye, axial length could also be shown to be a weak determinant of relative peripheral corneal thickness in that univariate regression indicated lower CTPIs would be more likely seen in those with a greater axial length \( (P \geq 0.037) \). The strength of the associations, however, was rather weak \( (r \leq -0.215) \), and CTPI was also not obviously linked to manifest refractive error, to anterior corneal curvature, or ACD \( (P \geq 0.490) \).

**Determinants of the Relative Peripheral Corneal Thicknesses: Multivariate Analyses of the CTPIs**

In a series of stepwise multivariate regression analyses, the combined contribution of age and posterior radius gave the strongest prediction of peripheral corneal thinning \( (R^2 = 0.459 \text{nasal}, R^2 = 0.341 \text{temporal}; \text{Table 2}) \), and with no further obvious or predictable contribution from corneal diameter or axial length (partial correlation, \( P \geq 0.425 \)). Stated another way, the age-dependent relative decrease in peripheral corneal thickness at 4 mm was still detectable, and still statistically significant, when any obvious causes of differences or variability in peripheral corneal thickness were considered (e.g., posterior corneal radius, HCD and axial length). Factoring in the HCD did not reduce the overall coefficient of determination, but it was shown to be a noncontributing factor (e.g., partial \( r = 0.079 \), \( P = 0.452 \) for 4 mm nasal location). The same applied to axial length and ACD. A separate series of step-wise regressions were made in various orders, to confirm the dominance of the posterior radius of curvature as the second major determinant of CTPIs (not shown).

Subjects with a history of contact lens wear or even current soft contact lens wear showed no difference in CTPI, either nasally or temporally, in comparison with non-contact lens wearers \( (P \geq 0.35) \).

**DISCUSSION**

The present study confirms and greatly extends earlier conclusions\(^5\) that there can be a predictable age-related thinning of the peripheral parts of the human cornea, when such a thinning is not evident at the center. The more peripheral corneal thicknesses are considered to be of importance in corneal transplantation\(^8\) and can be used to distinguish between keratoconus and normal corneas\(^12,15–17\) and also in assessments of contact lens–induced swelling of the cornea.\(^12,18\) The present study highlights the need for much further research in this aspect of the cornea.

In the present study, the geometric center of the cornea was selected as the reference central thickness. This selection has since been recommended for the acquisition of reliable and repeatable measurements of both central and peripheral locations.\(^15,19,20\) Overall, slightly different results can be obtained if
either a pupil centration or the thinnest (lowest) measure of corneal thickness within the central zone is used in the calculation of the CTPI. The overall outcome, however, is unchanged (unpublished analyses), largely because the magnitude of any differences for intact and largely healthy corneas is small. For example, as also indicated in other recent studies using both Orbscan and Pentacam, the net difference between the thickness at the vertex and the thinnest point of the cornea is likely to be less than 0.015 mm. Such differences are slightly larger than the expected repeatability of CCT measures with Orbscan, but further detailed studies and analyses are needed to define the thinnest region of the normal cornea.

The CCT data from the present study, of a cohort of white European individuals, are in agreement with a conclusion either a pupil centration or the thinnest (lowest) measure of corneal thickness within the central zone is used in the calculation of the CTPI. The overall outcome, however, is unchanged (unpublished analyses), largely because the magnitude of any differences for intact and largely healthy corneas is small. For example, as also indicated in other recent studies using both Orbscan and Pentacam, the net difference between the thickness at the vertex and the thinnest point of the cornea is likely to be less than 0.015 mm. Such differences are slightly larger than the expected repeatability of CCT measures with Orbscan, but further detailed studies and analyses are needed to define the thinnest region of the normal cornea.

The CCT data from the present study, of a cohort of white European individuals, are in agreement with a conclusion

![Figure 4](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933451/)

**Figure 4.** Scatterplots to show age-related differences in relative CTPIs for (A) temporal 2.5 mm from center, (B) nasal 2.5 mm from center, (C) temporal 3 mm from center, (D) nasal 3 mm from center, (E) temporal 4 mm from center, and (F) nasal 4 mm from center. The number of data points is reduced to 104 in (D) and to 94 in (F). The lines are from a linear regression analysis.

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Posterior radius of curvature</td>
<td></td>
</tr>
<tr>
<td>HCD</td>
<td></td>
</tr>
<tr>
<td>Axial length</td>
<td></td>
</tr>
</tbody>
</table>

The results are from univariate linear regression with the Pearson's correlation coefficient ($r$). All regressions yielded statistically significant outcomes ($P < 0.05$).
The results are from stepwise multivariate linear regression with the coefficient of determination ($R^2$). All regressions yielded statistically significant outcomes ($P < 0.05$). AL, axial length.

The coefficient of determination ($R^2$). All regressions yielded statistically significant outcomes ($P < 0.05$). AL, axial length.

The coefficient of determination ($R^2$). All regressions yielded statistically significant outcomes ($P < 0.05$). AL, axial length.

drawn from a previous meta-analysis\(^2\) as well as related studies on white European children and middle-aged and elderly adults.\(^3,23\) This overall conclusion was that little or no change in CCT would be expected after the early childhood years (where substantial growth is still occurring). For nonwhite adult individuals, however, several studies have indicated an age-related decline in CCTs.\(^2\) From studies that likely included a proportion of white individuals, different techniques and statistical approaches have been used to assess CCT (Table 3).

As with the present study, all the other published studies have been cross-sectional. Some studies have applied a linear regression model to the CCT data,\(^5,10,24–29\) whereas others have assessed whether statistical differences could be detected between individuals grouped by age-related decades.\(^3,19,30–32\) The outcomes were whether the slope of a regression analysis was greater than 0 ($P < 0.05$) or whether different groups were significantly different ($P < 0.05$). The outcome of most studies, including the present one, has been that there was no predictable effect of age on central corneal thickness in adults. In another study using Orbscan, it was briefly noted that a very slight age-related increase in CCT was observed.\(^7\) However, several other factors could also determine or influence CCT.\(^2,24\) These include corneal curvature and axial length, as well as refractive error as nonpathologic entities. For the present cohort, as likely for most of those previously published, a weakness in the sample cohort was that refractive error was not controlled for. Although, for the present cohort, every effort was made to exclude any individual with any notable posterior segment abnormalities indicative of myopia-related stretching of the eye, it is acknowledged that a different result, at least for central corneal thickness and age, might have been seen if only emmetropic subjects had been recruited, although numerous multivariate analyses failed to indicate any substantial predictive effect of either refractive error (or its major anatomic correlate, the axial length) on CTPI. However, if a progressive age-related decrease in CCT can be confirmed as a predictable characteristic of emmetropic Caucasian adults,\(^29\) then it should be established how large or small such an age-related effect might be in myopic individuals being considered for refractive surgery.

As an anatomic variable that would be expected to be associated with refractive error and axial length, ACD measures could also be included in the type of multivariate analyses used in this study. No outcome was obtained that would indicate that those eyes with a shallower or those with a deeper anterior chamber had any difference in either CCT, peripheral thickness, or CTPI. However, it is likely that the cohort studied is not really suitable for undertaking such analyses, and it would be useful, for example, to assess age-matched hyperopic versus emmetropic groups. It is acknowledged that ACD can change substantially in diseased eyes, such as those with angle-closure glaucoma,\(^24\) and such a condition can also produce corneal edema and thus a measurable increase in CCT.\(^2\) Acutely elevated IOP could cause increased thickness as a result of pressure-induced endothelial dysfunction, and this

### Table 2. Combined Determinants of Relative CTPI

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>$R^2$ (Nasal)</th>
<th>$R^2$ (Temporal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age + posterior radius of curvature</td>
<td>0.459</td>
<td>0.341</td>
</tr>
<tr>
<td>Age + posterior radius + HCD</td>
<td>0.462</td>
<td>0.344</td>
</tr>
<tr>
<td>Age + posterior radius + HCD + AL</td>
<td>0.464</td>
<td>0.346</td>
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### Table 3. Summary of Detailed Studies CCT and Age in (Presumably) Caucasian Individuals

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Ref.</th>
<th>Age Range (y)</th>
<th>Method</th>
<th>Eyes (n)</th>
<th>Age Effect</th>
<th>$P$</th>
<th>$r$</th>
<th>Notes</th>
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<tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Martola</td>
<td>1968</td>
<td>4</td>
<td>10–90</td>
<td>SL</td>
<td>209</td>
<td>No</td>
<td>$&gt;0.05$</td>
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<td>*</td>
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<tr>
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<td>1969</td>
<td>24</td>
<td>23–77</td>
<td>SL</td>
<td>157</td>
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<td>$&gt;0.05$</td>
<td>0.087</td>
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<tr>
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<td>10–90</td>
<td>SL</td>
<td>76</td>
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<tr>
<td>Korey</td>
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<td>21</td>
<td>22–78</td>
<td>SL</td>
<td>103</td>
<td>No</td>
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<td></td>
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<tr>
<td>Carlson</td>
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<td>5–79</td>
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<td>Cox</td>
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<td>27</td>
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<td>No</td>
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<tr>
<td>Rapuano</td>
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<td>9–80</td>
<td>SL</td>
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<td>No</td>
<td>$&gt;0.05$</td>
<td></td>
<td>†</td>
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<tr>
<td>Siu</td>
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<td>17–75</td>
<td>US</td>
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<td>No</td>
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<td>0.04</td>
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</tr>
<tr>
<td>Wolfs</td>
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<td>365</td>
<td>No</td>
<td>0.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanches-Gimeno</td>
<td>2004</td>
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<td>US</td>
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<td>&lt;0.001</td>
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<td>Pentacam</td>
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<td>8</td>
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<td>777</td>
<td>Yes?</td>
<td>$&gt;0.03$</td>
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<td>18–82</td>
<td>Orbscan</td>
<td>109</td>
<td>Yes</td>
<td>&lt;0.036</td>
<td>-0.21</td>
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<td><strong>Peripheral Corneal Thickness</strong></td>
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<td>Martola</td>
<td>1968</td>
<td>4</td>
<td>10–90</td>
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<td>209</td>
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<td>5</td>
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<td>US</td>
<td>108</td>
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<td>NA</td>
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<td>Orbscan</td>
<td>109</td>
<td>Yes</td>
<td>&lt;0.036</td>
<td>-0.21</td>
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Where regression analyses were reported, the significance ($P$) and correlation coefficients ($r$) are given. US, ultrasound pachymetry; SL, slit lamp-based optical pachymetry; SM, specular microscopy.

For those studies where discrete age groups were compared:  
* No statistically significant difference was detected between seven different age groups.
† No difference was detected between nine different age groups.  
‡ Compared those age >40 years with younger individuals, but also there were no significant differences ($P > 0.05$) when comparing groups by decade.  
§ Compared nine different age groups.  
|| Absolute thicknesses at 4 mm. If considered relative to CCT values, the difference at 4 mm was much greater ($P < 0.001$, $r \approx -0.362$).
increase might persist for quite a while after the IOP has been reduced with medical therapy or surgery. Although there is limited evidence that long-term use of topical hypotension medications are associated with lowered IOP and very slight reduction in CCT, the predominant IOP-CCT interaction is that of differences in CCT resulting in differences in the outcome of tonometry. Although this effect can be substantial and can be readily demonstrated with Orbscan pachymetry, it is not logical to consider IOP to be a determinant of CCT in generally healthy eyes. For this reason, IOP was not considered in the multivariate regressions.

For the cohort evaluated in the present study, recruited as a nonrandom sample but with a reasonable balance across the adult age spectrum, a just-detectable, age-related difference (thinner relative thicknesses) was noted at 2.5 mm nasally from the center point and a frank statistically significant difference at 4 mm from the center. That an age-related difference in absolute thicknesses is not substantial in the mid-periphery is consistent with another Orbscan-based study, where analysis of the thickness averaged over 2-mm diameter zones in the mid-periphery indicated an age-related decline in thickness (P = 0.00, r = −0.3) on the nasal side but not the temporal side of the cornea. Similarly, another recent study by the same group with the Pentacam system reported only very slight reductions in absolute thicknesses in the nasal mid-periphery (P = 0.04, r = −0.16). The present studies were undertaken with Orbscan, an instrument and procedure that generates different CCTs from other optical or ultrasound pachymetry methods, with the differences between Orbscan and ultrasound measures, for example, getting progressively greater away from the corneal center. As discussed in these papers, one can argue that the Orbscan data are artifactually too high or that the ultrasound pachymetry measures are too low, although the reproducibility of both methods are comparable at both the central and peripheral sites. Orbscan, therefore, will likely produce systematically higher CTPIs than those obtained with at least some ultrasound pachymeters. However, as detailed in Table 3, the relative peripheral thinning of the cornea that can occur has been assessed with both slit lamp and ultrasound pachymetry. In terms of the general repeatability of peripheral Orbscan measures and its impact on CTPIs, a 1% or even a 1.5% error in Orbscan thickness estimates at 3.5 or 4 mm from center would obviously have an impact of approximately 0.015 on CTPI estimates (i.e., a CTPI could change from 1.200 to either 1.185 or 1.215). However, analysis of repeatability in relation to age revealed no significant trends (P ≥ 0.05).

The apparent, albeit small, differences in the symmetry and predictability of the peripheral corneal thinning effect, could reflect a natural anatomic difference in human corneas or could be considered as some form of artifact. As acknowledged elsewhere, it is harder to obtain consistent sets of true peripheral thickness data on the nasal side of the cornea. Either way, a complete symmetry to the peripheral thinning should not be presumed and could, for example, be dependent on refractive error. If any type of refractive error-related difference in CTPI were present, then this could be highly relevant to both refractive surgery and corneal grafting. Incorporating the posterior curvature into calculations of corneal power, rather than just relying on topographic surface profile and/or the anterior corneal curvature, has included considerations of thickness of the mid-peripheral cornea and so it would be logical to extend this to closer to the true periphery of the cornea.

Since the central corneal thicknesses did not show any detectable age-related difference, any thinning trend at more peripheral locations means that the relative difference between central and peripheral thickness is less. This difference is highlighted by specifically comparing different peripheral to central thicknesses by the corneal thickness profile index or CTPI. The mean CTPI (4 mm) was marginally higher on the nasal aspect at 1.21 compared with that on the temporal aspect of the cornea (1.19). A similar calculation has been used, referred to as the P-C ratio, but either compared the temporal cornea to the center, or an average of four peripheral thicknesses to the center measure. The relative location of peripheral measures in these two studies were probably very similar. For the present cohort, however, there was a very small asymmetry in CTPI (nasal versus temporal) that was statistically significant (P = 0.001), so the age-related effects on peripheral corneal thickness may actually be slightly greater than those reported previously because the effects appeared to be slightly greater nasally. Any net difference between peripheral corneal and more central thicknesses, as detected by Orbscan, could arise because of actual differences in tissue thickness or because the Orbscan system has yielded erroneous measures. Abnormal light-scattering characteristics (designated as corneal haze) have been indicated as the cause of unusually low corneal thickness readings with Orbscan. In some elderly individuals, the peripheral zone of the cornea may be affected by lipid deposits, as in the corneal arcus. One elderly subject, not included in the current analyses, had a very notable arcus, and few Orbscan data points were obtained beyond the mid-periphery of the cornea (i.e., this type of alteration in light-scattering of the cornea could result in no data from these sites). With the expected location and width of the corneal arcus, with respect to the HCD, only extreme cases would be likely to encroach into the peripheral 4-mm zone mapped by Orbscan. This limitation could affect the nasal and temporal aspects, as well as superior or inferior peripheral zones, and so is not an obvious reason for why nasal 4-mm readings are more difficult to obtain with Orbscan.

The present analyses, especially the stepwise regression, indicate that the age-related peripheral thinning and the peripheral-to-central difference in thickness are related to the posterior curvature of the cornea. A previous analysis of a similar cohort (i.e., age, 23–77 years) considered only CCT and posterior curvature. In the present analyses, nasal CTPI was used as the dependent variable and included the two strongest correlates from the univariate analyses (i.e., age and posterior radius of curvature), as independent predictive factors. The model accounted for approximately 46% of the variance in nasal CTPI (R² = 0.459). Inclusion of HCD in the model led only to a slightly higher coefficient of determination (R² = 0.462). The partial correlation coefficients indicated that age and posterior radius were the two variables that were still associated with nasal CTPI when the remaining variables were kept constant (P < 0.001, r = −0.599 and P < 0.001, r = −0.414, respectively).

**CONCLUSION**

A relative thinning of the peripheral cornea with increasing age was noted in the present studies. The finding of peripheral corneal thinning in generally normal adults could potentially be important when assessing individuals for refractive surgery procedures and also when matching donor corneas to recipients. This result was obtained using the Orbscan scanning slit system, and it is important to find out whether the same or similar peripheral thinning can be seen with rotary image acquisitions and analysis software using single (Pentacam; Oculus) or dual (Galilei; Zeimer Group, Port, Switzerland) light-projection systems. The latter systems may allow these types of analyses to be extended even farther out (i.e., to 5 mm either side of center) and further studies will clearly be most useful.
Acknowledgments

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References