Parapapillary Beta Zone and Gamma Zone in a Healthy Population: The Beijing Eye Study 2011

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Purpose. To assess prevalence and size of the parapapillary beta zone and gamma zone in a healthy population.

Methods. Within the population-based Beijing Eye Study, individuals without retinal or optic nerve disease were selected. Using optical coherence tomography (OCT), we measured the parapapillary beta zone (defined by presence of Bruch’s membrane and absence of RPE) and gamma zone (region between Bruch’s membrane end and optic disc border).

Results. The study included 723 individuals (mean age: 59.5 ± 7.6 years; range: 50–90 years). The beta zone was detected in 525 eyes (72.6%; 95% confidence interval [CI]: 69.4, 75.9). A larger maximum width of the beta zone (mean: 253 ± 225 μm) was associated (multivariate analysis; regression coefficient $r^2$: 0.56) with older age ($P < 0.001$; standardization regression coefficient beta: 0.28), thinner temporal parapapillary choroidal thickness ($P < 0.001$; beta: −0.21), longer axial length ($P < 0.001$; beta: 0.14), longer vertical Bruch’s membrane opening (BMO) length ($P < 0.001$; beta: 0.32), shorter horizontal BMO length ($P = 0.003$; beta: −0.12), and more pronounced vertical optic disc rotation of ($P < 0.001$; beta: 0.15). The gamma zone was detected in 190 eyes (26.3 ± 1.6%; 95% CI: 23.1, 29.5). A larger maximal width of the gamma zone (mean: 86 ± 187 μm) was ($r^2$: 0.49) associated with longer axial length ($P < 0.001$; beta: 0.46), thinner central corneal thickness ($P < 0.001$; beta: 0.10), thinner temporal parapapillary choroidal thickness ($P < 0.001$; beta: −0.11), longer vertical ($P < 0.001$; beta: 0.15), and horizontal ($P = 0.02$; beta: 0.08) BMO length, and more pronounced vertical rotation of optic disc ($P < 0.001$; beta: 0.32).

Conclusions. As measured by OCT in this healthy adult Chinese population, the gamma zone was mainly associated with longer axial length but not with age, while the beta zone was correlated mainly with older age and also with axial length. Both zones were largest in the temporal parapapillary region and smallest in the nasal region.

Keywords: parapapillary beta zone, beta zone, glaucoma, parapapillary gamma zone, optical coherence tomography, optic nerve head, optic nerve, optic disc, myopia

The parapapillary region of the optic nerve head has recently been divided into four zones.1–20 Alpha zones were characterized by the presence of Bruch’s membrane and absence of an irregularly structured RPE. Upon ophthalmoscopy, it appeared as an irregular hypopigmentation and hyperpigmentation and, compared with any other parapapillary zone, it was located most distant from the optic disc. The beta zone, defined by the presence of Bruch’s membrane and absence of RPE, was a whitish zone upon ophthalmoscopy and showed large choroidal vessels and the sclera. It was located at the inner border of the alpha zone in the same direction as the optic disc. In the gamma zone, Bruch’s membrane was absent, explaining that the RPE and the choriocapillaris were additionally missing. The delta zone, a part of gamma zone, was located at the border of the optic disc (defined as the end of the lamina cribrosa) on an elongated and thinned parapapillary scleral flange in highly myopic eyes. In the delta zone, the orbital cerebrospinal fluid space was separated from the intravitreal compartment just by the elongated and thinned peripapillary scleral flange and the overlying retinal nerve fibers.1 Histologic and hospital-based clinical studies have suggested that the beta zone as defined above was associated mainly with glaucoma and to a lower degree with axial myopia, while the gamma zone was strongly correlated with axial elongation and myopic maculopathy and less marked with glaucoma.2–6,10,11–15,18–20

The limitations of these studies were that their study population was highly selected, either by the underlying disease, which led to the enucleation of the globe in the histologic investigations, or due to the inclusion criteria of the hospital-based studies. To assess the potential value of the beta and gamma zones in the diagnosis of glaucoma and other ocular disorders, it is therefore helpful to know the prevalence and size of both zones in a healthy, randomly selected study population without ocular diseases. We thus conducted the present study to assess the prevalence and to measure the size of beta zone and gamma zone in individuals without any disease
of the retina or optic nerve and participating in a study with a population-based recruitment of the participants.

METHODS

The Beijing Eye Study is a population-based study that was performed in Greater Beijing and included an urban part and a rural part. According to the declaration of Helsinki, the Medical Ethics Committee of the Beijing Tongren Hospital approved the study protocol and all study participants gave their written informed consent. The only eligibility criteria for the study were living in the study region and having an age of 50 years or older in the year 2011. Of 4403 eligible individuals, 3468 (78.8%) subjects (1963 [57.7%] women) participated. The mean age was 64.6 ± 9.8 years (median 64 years; range, 50–93 years). There were 1635 (47.1%) individuals (943 [57.7%] women) coming from the rural region, with the remaining 1835 (52.9%) study participants (1020 [55.6%] women) living in the urban region. The study population and the study design have been described in detail previously.21,22

For the purpose of the present study, we excluded eyes with any disease of the retina or optic nerve, including any type of glaucoma, diabetic retinopathy, status after an ocular trauma or retinal detachment, retinal vein occlusions, AMD, and any other maculopathy. Inclusion criterion was a best refractive error (spherical equivalent) ranging between −1.0 and −4.00 diopters (D), and a best-corrected visual acuity of 20/25 or better for eyes with a refractive error of less than −4.00 D. We randomly selected 500 eyes and 50 eyes with the refraction within ±1.00 D and less than −1 to −2 D, respectively (almost half of each subgroup). All eyes with a refractive error of less than −2 D were enrolled. In the final step, the enrolled eyes were stratified according to their refractive error into the groups of emmetropia (−1 to +1 D), minor myopia (<−1 to −3 D), moderate myopia (<−3 to −6 D), and high myopia (myopia >−6 D).

The optic nerve head, including the peripapillary area, was imaged by spectral-domain optical coherence tomography (OCT; Spectralis; Heidelberg Engineering Co., Heidelberg, Germany). The optic disc scan protocol included six radial scan lines with a scan length of 6 mm, centered on the optic disc, and each comprising 100 A-scans. The parapapillary region was examined with the intrinsic viewer (Heidelberg Eye Explorer software version 1.7.0.0; Heidelberg Engineering), which automatically synchronized the vertical lines of each B-scan and the infrared image taken by the OCT device. The parapapillary beta zone was defined as the region between Bruch’s membrane opening (i.e., the end of Bruch’s membrane) and the start of the RPE on Bruch’s membrane (Figs. 1–3). In eyes in which the end of Bruch’s membrane did not reach the optic disc border (defined by the peripapillary border tissue of Jacoby and Elschnig), the parapapillary gamma zone was defined as the region between the end of Bruch’s membrane and the border of the optic disc (Figs. 2, 3). Images with a magnification of up to 200% were examined by a trained examiner (QZ). The locations of the largest part of the beta and gamma zones were recorded. To assess the reproducibility of the measurements, the OCT images of 50 eyes were randomly selected and remeasured in a masked manner with an interval of 2 weeks.

Using the enhanced-depth imaging modality, we additionally obtained seven OCT sections (each comprising 100 averaged scans) in a 5° × 30° large rectangle centered onto the fovea. Using the scan running through the foveola, we measured the thickness of the subfoveal choroid and the length of Bruch’s membrane from the foveola to the end of Bruch’s membrane in direction of the optic nerve head.20,21 The thickness of the parapapillary choroid was measured on a circular OCT scan with a diameter of 3.4 mm around the optic nerve head center.23 The rotation of the optic disc around the vertical optic disc axis and the optic disc rotation around the horizontal disc axis was assessed on OCT scans, which ran through the center on the optic nerve head in the horizontal direction and in the vertical direction (Fig. 3).23–25 We determined the angle between the line connecting the ends of Bruch’s membrane and the horizontal for the measurement of the optic disc rotation around the vertical disc axis, and we assessed the angle between the line connecting the Bruch’s membrane ends and the vertical for the determination of the optic disc rotation around the horizontal disc axis.
Beta Zone and Gamma Zone in a Healthy Population

The statistical analysis was performed using a commercially available statistical software package (SPSS for Windows, version 22.0; IBM-SPSS, Chicago, IL, USA). In a first step of the analysis, we calculated the mean and SD and medians and ranges of the main outcome parameters (i.e., prevalence and size of the beta and gamma zones). In a second step, we performed a univariate analysis to assess associations between the prevalence and width of the parapapillary beta zone (and gamma zone) and other ocular and systemic parameters. In a third and final step, we carried out a multivariate analysis, in which the list of independent parameters included all variables that were significantly associated with the parapapillary beta zone (and gamma zone) in the univariate analysis. We then dropped step by step those independent parameters that were no longer significantly associated with the beta zone (and gamma zone). We presented 95% confidence intervals (CI). All $P$ values were two-sided and considered statistically significant when they were less than 0.05.

Results

The OCT images for 723 right eyes of 723 individuals (420 [58.1%] women) were enrolled for the measurement of the beta and gamma zones. The mean age was 59.5 ± 7.6 years (median: 58 years; range, 50–90 years), the mean refractive error (spherical equivalent) was $-0.97 \pm 2.08$ diopters (median: $-0.13$ D; range, $-12.5$ to $+1.00$ D), and the mean axial length was $23.54 \pm 1.26$ mm (median: $23.25$ mm; range, $20.88$–$29.86$ mm) (Table 1).

The beta zone was detected in 525 eyes (72.6%; 95% CI: 69.4, 75.9%; Table 1). In univariate analysis, its prevalence increased significantly with the systemic parameters of older age ($P < 0.001$), male sex ($P = 0.001$), urban region of habitation ($P < 0.001$), lower body mass index ($P = 0.003$), taller body height ($P = 0.03$), and higher blood concentration of creatinine ($P = 0.001$); and with the ocular parameters of longer axial length ($P < 0.001$), more myopic refractive error ($P < 0.001$), longer anterior corneal curvature ($P = 0.001$), thinner subfoveal choroidal thickness ($P < 0.001$), thinner parapapillary temporal choroidal thickness ($P < 0.001$), higher degree of parapapillary ($P < 0.001$) and macular ($P < 0.001$) fundus tessellation, and longer Bruch’s membrane opening length ($P < 0.001$). The prevalence of the beta zone was not significantly associated with the systemic parameters of level of education ($P = 0.07$), body weight ($P = 0.28$), body hip circumference ($P = 0.10$), body waist circumference ($P = 0.46$), cognition function score ($P = 0.47$), prevalence of intake of aspirin ($P = 0.47$), blood concentrations of glucose ($P = 0.88$), glycosylated hemoglobin HbA1c ($P = 0.53$), high-density lipoproteins ($P = 0.79$), low-density lipoproteins ($P = 0.99$), triglycerides ($P = 0.27$), cholesterol ($P = 0.94$) and C-reactive protein ($P = 0.99$), systolic ($P = 0.44$), diastolic ($P = 0.75$), or mean ($P = 0.86$) blood pressure, heart pulse ($P = 0.13$), prevalence of diabetes mellitus ($P = 0.54$) and arterial hypertension ($P = 0.82$), package years of smoking ($P = 0.23$), prevalence of ever smoking ($P = 0.19$), or current smoking ($P = 0.41$); and the ocular parameters of cylindrical refractive error ($P = 0.08$), central corneal thickness ($P = 0.14$), anterior chamber depth ($P = 0.44$), lens thickness ($P = 0.09$), IOP ($P = 0.41$), and optic disc rotation around the vertical ($P = 0.78$) and horizontal axis ($P = 0.66$).

The multivariate analysis included the prevalence of the beta zone as a dependent variable, and as independent variables all those parameters that were significantly associated with the prevalence of the beta zone in the univariate analysis. Due to a lack of significance, we dropped the parameters of blood concentration of creatinine ($P = 0.93$), refractive error ($P = 0.98$), body height ($P = 0.87$), body mass index ($P = 0.60$), central corneal thickness ($P = 0.55$), fundus tessellation (macula and optic disc combined; $P = 0.18$), subfoveal choroidal thickness ($P = 0.22$), and urban region of habitation ($P = 0.05$). In the final model, a higher prevalence of the beta zone was associated (Nagelkerke $R^2: 0.23$) with older age ($P < 0.001$), male sex ($P = 0.05$), thinner temporal choroidal thickness ($P < 0.001$), larger anterior corneal curvature radius ($P = 0.01$), and longer diameter of the optic disc Bruch’s membrane opening ($P < 0.001$; Table 2)
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Emmetropia (−1 to +1 D)</th>
<th>Minor Myopia (&lt;−1 to &lt;−3 D)</th>
<th>Moderate Myopia (&lt;−3 to &lt;−6 D)</th>
<th>High Myopia (&gt;−6 D)</th>
<th>All Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>500</td>
<td>93</td>
<td>102</td>
<td>28</td>
<td>723</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.2 ± 6.7 (50–82)</td>
<td>61.0 ± 8.4 (50–85)</td>
<td>64.5 ± 8.1 (50–90)</td>
<td>60.9 ± 9.9 (50–87)</td>
<td>59.5 ± 7.6 (50–90)</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>195/305</td>
<td>51/42</td>
<td>46/56</td>
<td>11/17</td>
<td>303/420</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>23.0 ± 0.8</td>
<td>23.8 ± 1.1</td>
<td>25.2 ± 1.0</td>
<td>26.0 ± 2.0</td>
<td>23.5 ± 1.3</td>
</tr>
<tr>
<td>Optic disc rotation around the vertical disc axis, degree</td>
<td>1.25 ± 2.51</td>
<td>1.37 ± 3.24</td>
<td>2.99 ± 3.61</td>
<td>3.53 ± 3.26</td>
<td>1.60 ± 2.90</td>
</tr>
<tr>
<td>Optic disc rotation around the horizontal disc axis, degree</td>
<td>1.77 ± 1.60</td>
<td>2.09 ± 2.06</td>
<td>1.68 ± 2.82</td>
<td>4.98 ± 9.16</td>
<td>1.92 ± 2.61</td>
</tr>
<tr>
<td>Macular Bruch’s membrane length, mm</td>
<td>4.65 ± 0.30</td>
<td>4.66 ± 0.44</td>
<td>4.47 ± 1.29</td>
<td>4.67 ± 0.60</td>
<td>4.64 ± 0.54</td>
</tr>
<tr>
<td>Prevalence of beta zone</td>
<td>344/500 (68.8%)</td>
<td>69/93 (74.2%)</td>
<td>85/102 (83.3%)</td>
<td>27/28 (96.4%)</td>
<td>525/23 (72.6%)</td>
</tr>
<tr>
<td>Width of beta zone, μm</td>
<td>208 ± 177 (0–980)</td>
<td>281 ± 220 (0–1059)</td>
<td>392 ± 303 (0–1595)</td>
<td>453 ± 332 (0–1546)</td>
<td>253 ± 225 (0–1595)</td>
</tr>
<tr>
<td>Location of beta zone (temporal/inferior/superior)</td>
<td>301 (87.5%) eyes/28 (8.1%)</td>
<td>62 (89.9%) eyes/4 (5.8%)</td>
<td>73 (85.9%) eyes/7 (8.2%)</td>
<td>23 (85.2%) eyes/2 (7.4%)</td>
<td>459 (87.4%) eyes/41 (7.8%)</td>
</tr>
<tr>
<td>Prevalence of gamma zone</td>
<td>84/500 (16.8%)</td>
<td>28/93 (30.1%)</td>
<td>59/102 (57.8%)</td>
<td>19/28 (67.9%)</td>
<td>190/723 (26.3%)</td>
</tr>
<tr>
<td>Width of gamma zone, μm</td>
<td>32 ± 82 (0–546)</td>
<td>90 ± 159 (0–724)</td>
<td>243 ± 262 (0–890)</td>
<td>460 ± 420 (0–1646)</td>
<td>86 ± 187 (0–1646)</td>
</tr>
<tr>
<td>Location of gamma zone (temporal/inferior/nasal)</td>
<td>42 (50%) eyes/37 (44.1%)</td>
<td>18 (64.3%) eyes/9 (32.1%)</td>
<td>32 (54.2%) eyes/26 (44.1%)</td>
<td>7 (56.8%) eyes/11 (57.9%)</td>
<td>99 (52.1%) eyes/85 (43.7%)</td>
</tr>
<tr>
<td>Macular Bruch’s membrane length, mm</td>
<td>4.65 ± 0.30</td>
<td>4.66 ± 0.44</td>
<td>4.47 ± 1.29</td>
<td>4.67 ± 0.60</td>
<td>4.64 ± 0.54</td>
</tr>
</tbody>
</table>
The mean largest width of the beta zone was 253 ± 225 μm (median: 243.0 μm; range, 0–1595 μm). In univariate analysis, a larger width of the beta zone was significantly associated with older age (P < 0.001), male sex (P = 0.003), urban region of habitation (P < 0.001), higher level of education (P = 0.001), lower body mass index (P < 0.001), lower diastolic blood pressure (P = 0.04), and higher blood concentration of creatinine (P = 0.005); and with the ocular parameters of longer axial length (P < 0.001; Fig. 4), more myopic refractive error (P < 0.001), higher amount of cylindrical refractive error (P < 0.001), longer anterior corneal curvature (P = 0.002), deeper anterior chamber depth (P = 0.02), thicker lens thickness (P = 0.004), thinner subfoveal choroidal thickness (P < 0.001), thinner parapapillary choroidal thickness (P < 0.001), higher degree of parapapillary (P < 0.001) and macular (P < 0.001) fundus tessellation, longer horizontal Bruch’s membrane opening length (P < 0.001), and larger optic disc rotation around the vertical (P < 0.001) and horizontal axis (P = 0.04). A larger width of the beta zone was not significantly associated with body height (P = 0.11), blood concentrations of glucose (P = 0.96), glycosylated hemoglobin HbA1c (P = 0.39), high-density lipoproteins (P = 0.36), low-density lipoproteins (P = 0.92), triglycerides (P = 0.41), cholesterol (P = 0.87) and C-reactive protein (P = 0.94), systolic (P = 0.92) or mean (P = 0.26) blood pressure, heart pulse (P = 0.22), prevalence of diabetes mellitus (P = 0.06) and arterial hypertension (P = 0.25), package years of smoking (P = 0.46), prevalence of ever smoking (P = 0.75), or current smoking (P=0.29), intake of aspirin (P = 0.25), and current alcohol consumption (P = 0.99) and amount of alcohol consumption (P = 0.37); and the ocular parameters of central corneal thickness (P = 0.14), and IOP (P = 0.49).

In the multivariate analysis, we dropped due to collinearity the parameters of refractive error (variance inflation factor [VIF]: 6.3), anterior chamber depth (VIF: 2.7), and subfoveal choroidal thickness (VIF: 3.0). Due to a lack of significance, we then dropped fundus tessellation (P = 0.99), body mass index (P = 0.86), sex (P = 0.78), diastolic blood pressure (P = 0.56), level of education (P = 0.59), lens thickness (P = 0.33), blood concentration creatinine (P = 0.18), cylindrical refractive error (P = 0.62), region of habitation (P = 0.57), and anterior corneal curvature radius (P = 0.52). In the final model, a larger width of the beta zone was significantly (regression coefficient $r^2$, 0.36) associated with older age (P < 0.001), thinner temporal parapapillary choroidal thickness (P < 0.001), longer axial length (P < 0.001), longer vertical Bruch’s membrane opening length (P < 0.001), shorter horizontal Bruch’s membrane opening length (P = 0.003), and more pronounced rotation of optic disc around the vertical axis (P < 0.001; Table 3).

Among the eyes with the beta zone (n = 525), the largest width of the beta zone was located in the temporal region in 459 (87.4%) eyes, in the inferior region in 41 (7.8%) eyes, and in the superior area in 25 (4.8%) eyes. It was located in the nasal region in any of the eyes.

### Table 2. Associations (Multivariate Analysis) of the Prevalence of the Parapapillary Beta Zone in the Beijing Eye Study 2011

<table>
<thead>
<tr>
<th>Parameters</th>
<th>P Value</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>&lt;0.001</td>
<td>1.08</td>
<td>1.04, 1.11</td>
</tr>
<tr>
<td>Sex, men/women</td>
<td>0.03</td>
<td>0.63</td>
<td>0.42, 0.95</td>
</tr>
<tr>
<td>Anterior corneal curvature radius, mm</td>
<td>0.01</td>
<td>2.77</td>
<td>1.25, 6.17</td>
</tr>
<tr>
<td>Temporal parapapillary choroidal thickness, μm</td>
<td>&lt;0.001</td>
<td>0.994</td>
<td>0.991, 0.997</td>
</tr>
<tr>
<td>Optic nerve head Bruch’s membrane opening vertical diameter, μm</td>
<td>&lt;0.001</td>
<td>1.003</td>
<td>1.002, 1.004</td>
</tr>
</tbody>
</table>
The gamma zone was detected in 190 eyes (26.3%; 95% CI: 23.1, 29.5%; Table 1). In univariate analysis, the prevalence of the gamma zone increased significantly with the systemic parameters of older age \( (P = 0.02) \), male sex \( (P = 0.001) \), urban region of habitation \( (P < 0.001) \), higher level of education \( (P < 0.001) \), lower body mass index \( (P = 0.02) \), taller body height \( (P < 0.001) \), lower blood concentration of high-density lipoproteins \( (P = 0.04) \), and lower systolic blood pressure \( (P = 0.005) \), and mean \( (P = 0.006) \) blood pressure; and with the ocular parameters of longer axial length \( (P < 0.001) \), more myopic refractive error \( (P < 0.001) \), longer anterior corneal curvature \( (P = 0.001) \), thicker central corneal thickness \( (P < 0.001) \), deeper anterior chamber depth \( (P < 0.001) \), thicker central corneal thickness \( (P < 0.001) \), thinner subfoveal choroidal thickness \( (P < 0.001) \), thinner para-papillary choroidal thickness \( (P < 0.001) \), higher degree of parapapillary \( (P < 0.001) \) and macular \( (P < 0.001) \) fundus tessellation, longer vertical \( (P < 0.001) \) and horizontal \( (P < 0.001) \) Bruch’s membrane opening length, and larger rotation of optic disc around the vertical axis \( (P = 0.006) \) and the horizontal axis \( (P < 0.001) \), and cylindrical refractive error \( (P < 0.001) \). The prevalence of the gamma zone was not significantly associated with the systemic parameters of body weight \( (P = 0.61) \), body waist circumference \( (P = 0.48) \), cognition function score \( (P = 0.14) \), prevalence of intake of aspirin \( (P = 0.43) \), blood concentration of creatinine \( (P = 0.21) \), blood concentrations of glucose \( (P = 0.80) \), glycosylated hemoglobin HbA1c \( (P = 0.88) \), low-density lipoproteins \( (P = 0.45) \), triglycerides \( (P = 0.64) \), cholesterol \( (P = 0.30) \) and C-reactive protein \( (P = 0.11) \), heart pulse \( (P = 0.83) \), prevalence of diabetes mellitus \( (P = 0.16) \) and arterial hypertension \( (P = 0.15) \), package years of smoking \( (P = 0.95) \) and prevalence of current smoking \( (P = 0.18) \), consumption of alcohol \( (P = 0.21) \); and the ocular parameters of lens thickness \( (P = 0.99) \), and IOP \( (P = 0.08) \).

The multivariate analysis included the prevalence of the gamma zone as a dependent variable, and as independent variables all those parameters that were significantly associated with the prevalence of the gamma zone in the univariate analysis. Due to a lack of significance, we dropped the parameters of diastolic blood pressure \( (P = 0.50) \), systolic blood pressure \( (P = 0.74) \), age \( (P = 0.25) \), region of habitation \( (P = 0.77) \), anterior chamber depth \( (P = 0.38) \), fundus tessellation \( (P = 0.80) \), level of education \( (P = 0.99) \), body mass index \( (P = 0.68) \), blood concentration of high-density lipoproteins \( (P = 0.82) \), central corneal thickness \( (P = 0.18) \), subfoveal choroidal thickness \( (P = 0.36) \), body height \( (P = 0.14) \), temporal parapapillary choroidal thickness \( (P = 0.25) \), and optic disc rotation around the horizontal axis \( (P = 0.45) \). In the final model, higher prevalence of the gamma zone was significantly (Nagelkerke $R^2 = 0.34$) associated with longer axial length \( (P < 0.001) \), shorter corneal curvature radius \( (P = 0.002) \), longer horizontal \( (P = 0.003) \) and vertical \( (P = 0.02) \) diameter of Bruch’s membrane opening, more marked rotation of optic disc around the vertical axis \( (P = 0.04) \), and male sex \( (P = 0.01) \); Table 4).

The mean largest width of the gamma zone was 86 ± 187 μm (median: 0 μm; range, 0–1646 μm). In univariate analysis, a larger width of the gamma zone was significantly associated with older age \( (P = 0.001) \), male sex \( (P = 0.01) \), urban region of habitation \( (P < 0.001) \), higher level of education \( (P < 0.001) \), lower body mass index \( (P < 0.001) \), taller body height \( (P = 0.001) \), lower systolic blood pressure \( (P = 0.001) \) and mean \( (P < 0.001) \) blood pressure, and higher prevalence of diabetes mellitus \( (P = 0.02) \); and with the ocular parameters of longer axial length \( (P < 0.001) \); Fig. 5), more myopic refractive error \( (P < 0.001) \), higher amount of cylindrical refractive error \( (P < 0.001) \), longer anterior corneal curvature \( (P < 0.001) \), deeper anterior chamber depth \( (P < 0.001) \), thicker central corneal thickness \( (P < 0.001) \), thinner subfoveal choroidal thickness \( (P < 0.001) \), thinner parapapillary choroidal thickness \( (P < 0.001) \), higher degree of parapapillary \( (P < 0.001) \) and macular \( (P < 0.001) \) fundus tessellation, longer vertical \( (P < 0.001) \) and horizontal \( (P < 0.001) \) Bruch’s membrane opening length, and larger rotation of optic disc around the vertical axis \( (P = 0.006) \) and the horizontal axis \( (P < 0.001) \), and cylindrical refractive error \( (P < 0.001) \). The prevalence of the gamma zone was not significantly associated with body weight \( (P = 0.12) \), blood concentrations of glucose \( (P = 0.60) \), glycosylated hemoglobin HbA1c \( (P = 0.57) \), high-density lipoproteins \( (P = 0.53) \), low-density lipoproteins \( (P = 0.47) \), triglycerides \( (P = 0.57) \), cholesterol \( (P = 0.77) \), creatinine \( (P = 0.51) \), and C-reactive protein \( (P = 0.19) \), cognitive function score \( (P = 0.09) \), heart pulse \( (P = 0.74) \), prevalence of arterial hypertension \( (P = 0.14) \), package years of smoking \( (P = 0.29) \), prevalence of ever smoking \( (P = 0.89) \), or current smoking \( (P = 0.41) \), intake of aspirin \( (P = 0.54) \), and current alcohol consumption \( (P = 0.95) \) and amount of alcohol consumption \( (P = 0.75) \); and the ocular parameters of thicker lens thickness \( (P = 0.60) \).

The multivariate analysis, we dropped due to collinearity the parameters of refractive error (VIF: 4.1), systolic blood

### Table 4. Associations (Multivariate Analysis) of the Prevalence of the Parapapillary Gamma Zone in the Beijing Eye Study 2011

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial length, mm</td>
<td>&lt;0.001</td>
<td>2.63 2.14 3.24</td>
</tr>
<tr>
<td>Sex, men/women</td>
<td>0.01</td>
<td>0.58 0.38 0.89</td>
</tr>
<tr>
<td>Corneal curvature radius, mm</td>
<td>0.002</td>
<td>0.23 0.90 0.58</td>
</tr>
<tr>
<td>Vertical Bruch’s membrane opening diameter, μm</td>
<td>0.02</td>
<td>1.001 1.000 1.002</td>
</tr>
<tr>
<td>Horizontal Bruch’s membrane opening diameter, μm</td>
<td>0.003</td>
<td>1.002 1.001 1.003</td>
</tr>
<tr>
<td>Optic disc rotation around the vertical, degree</td>
<td>0.04</td>
<td>1.12 1.007 1.25</td>
</tr>
</tbody>
</table>


pressure (VIF: 3.1), diastolic blood pressure (VIF: 12.4), and subfoveal choroidal thickness (VIF: 2.6). Due to a lack of significance, we then dropped body mass index ($P = 0.96$), level of education ($P = 0.94$), mean blood pressure ($P = 0.81$), fundus tessellation ($P = 0.61$), cylindrical refractive error ($P = 0.51$), sex ($P = 0.27$), body height ($P = 0.23$), region of habitation ($P = 0.15$), prevalence of diabetes ($P = 0.13$), IOP ($P = 0.45$), corneal curvature radius (due to collinearity with axial length), anterior chamber depth ($P = 0.12$), and age ($P = 0.17$).

In the final model, a larger width of gamma zone was significantly (regression coefficient $r^2: 0.49$) associated with longer axial length ($P < 0.001$), thinner central corneal thickness ($P < 0.001$), thinner temporal parapapillary choroidal thickness ($P < 0.001$), longer vertical ($P < 0.001$) and horizontal ($P = 0.02$) Bruch’s membrane opening length, and more pronounced rotation of optic disc around the vertical axis ($P < 0.001$; Table 5).

Among the eyes with the gamma zone ($n = 190$), the largest width of the gamma zone was located in the temporal region in 99 (52.1%) eyes, in the inferior region in 83 (43.7%) eyes, in the superior area in 5 (2.6%) eyes, and in the nasal region in 3 (1.6%) eyes.

The analysis of the intraobserver variability revealed an intraclass correlation coefficient (ICC) of 0.988 (95% CI: 0.980, 0.993) for the largest beta zone width and of 0.929 (95% CI: 0.855, 0.966) for the location of largest beta zone, 0.991 (95% CI: 0.984, 0.995) for the largest gamma zone width and 0.983 (95% CI: 0.842, 0.993) of the location of largest gamma zone.

**DISCUSSION**

In this population-based study, the prevalence of the beta zone was 72.6% (95% CI: 69.4, 75.9) and the mean largest width of the beta zone was 253 ± 225 μm. A larger beta zone width was associated with older age, thinner temporal parapapillary choroidal thickness, longer axial length, longer vertical Bruch’s membrane opening length, shorter horizontal Bruch’s membrane opening length, and more pronounced rotation of optic disc around the vertical axis. The largest width of the beta zone was located most often in the temporal region (87.4% of eyes), followed by the inferior region (7.8%) and the superior area (4.8%). The prevalence of the gamma zone was 26.3% (95% CI: 23.1, 29.5) and the mean maximal width of the gamma zone was 86 ± 187 μm. A larger maximal width of the gamma zone

### Table 5. Associations (Multivariate Analysis) of the Width of the Parapapillary Gamma Zone in the Beijing Eye Study 2011

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$P$ Value</th>
<th>Standardized Coefficient Beta</th>
<th>Nonstandardized Coefficient B</th>
<th>95.0% Confidence Interval of B</th>
<th>Variance Inflation Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial length, mm</td>
<td>&lt;0.001</td>
<td>0.46</td>
<td>66.2</td>
<td>57.4, 75.1</td>
<td>1.21</td>
</tr>
<tr>
<td>Temporal peripapillary choroidal thickness, μm</td>
<td>&lt;0.001</td>
<td>−0.11</td>
<td>−0.28</td>
<td>−0.43, −0.13</td>
<td>1.16</td>
</tr>
<tr>
<td>Central corneal thickness, μm</td>
<td>&lt;0.001</td>
<td>0.10</td>
<td>0.56</td>
<td>0.25, 0.87</td>
<td>1.03</td>
</tr>
<tr>
<td>Bruch’s membrane opening horizontal length, μm</td>
<td>0.02</td>
<td>0.08</td>
<td>0.07</td>
<td>0.01, 0.14</td>
<td>1.59</td>
</tr>
<tr>
<td>Bruch’s membrane opening vertical length, μm</td>
<td>&lt;0.001</td>
<td>0.15</td>
<td>0.14</td>
<td>0.08, 0.21</td>
<td>1.55</td>
</tr>
<tr>
<td>Optic disc rotation around the vertical, degree</td>
<td>&lt;0.001</td>
<td>0.32</td>
<td>22.1</td>
<td>17.8, 26.4</td>
<td>1.18</td>
</tr>
</tbody>
</table>
was associated with longer axial length, thinner temporal parapapillary choroidal thickness, longer vertical and horizontal Bruch’s membrane opening length, and more pronounced rotation of optic disc around the vertical axis. Among the eyes with the gamma zone (n = 190), the largest width of the gamma zone was located in the temporal region in 99 (52.1%) eyes, in the inferior region in 83 (43.7%) eyes, in the superior area in 5 (2.6%) eyes, and in the nasal region in 3 (1.6%) eyes.

The results of the present study are in agreement with the findings obtained in previous anatomic- and hospital-based investigations that the parapapillary gamma zone is strongly associated with longer axial length and shows a relatively steep increase in its prevalence beyond an axial length of approximately 25 mm.1–12 In 2013, Kim and colleagues12 examined 161 patients with POAG who had a temporal parapapillary whitish zone (formerly called β-zone) with a minimal width of 200 μm. Kim and associates12 observed that the axial length was significantly (P < 0.001) longer and that age was significantly (P < 0.001) lower in the eyes without Bruch’s membrane at the optic disc border than in eyes with an intact Bruch’s membrane. In addition, the optic nerve heads in the eyes with Bruch’s membrane extending to the optic disc border had a nonoblique configuration in contrast to eyes without Bruch’s membrane at the disc border and showing an oblique configuration of their optic nerve heads. Kim and coworkers12 concluded that the beta zone (“parapapillary atrophy with intact Bruch’s membrane” as termed by Kim et al.12) may be associated mostly with older age, while the gamma zone (“parapapillary atrophy lacking Bruch’s membrane”) may be due to a scleral stretching associated with myopic elongation of the globe. In a previous histomorphometric study, in which the beta and gamma zones were measured upon light microscopy in enucleated human eyes, the prevalence of the gamma zone increased steeply beyond an axial length of approximately 26.5 mm.1 If one takes into account that in the latter study the sagittal globe diameter was measured upon light microscopy in enucleated human eyes, in the inferior region in 83 (43.7%) eyes, in the superior area in 5 (2.6%) eyes, and in the nasal region in 3 (1.6%) eyes.

The association between a higher prevalence and a larger size of the gamma zone and the rotation of the optic disc around the vertical fits with the results of other previous studies in which the gamma zone, as measured in fundus photographs, was strongly associated with the vertical rotation of the optic disc in highly myopic eyes.13–15 Both the beta and gamma zones were correlated with longer axial length. The association between a higher prevalence and a larger size of the gamma zone and the rotation of the optic disc around the vertical fits with the results of other previous studies in which the gamma zone, as measured in fundus photographs, was strongly associated with the vertical rotation of the optic disc in highly myopic eyes.13–15 Both the beta and gamma zones were correlated with longer axial length. In addition to the complete loss of RPE cells and incomplete loss of retinal photoreceptors, and that in the gamma zone, besides large choroidal vessels running from the peripapillary arterial circle of Zinn-Haller to the choroid, no other choroidal structures are present.1,2,17–22 The findings are also in agreement with recent optical coherence tomographic angiographic investigations.30,31
vertical axis and development and enlargement of the parapapillary gamma zone in children with incipient and progressive myopia. The finding that the gamma zone is associated only with a slight enlargement of the Bruch's membrane opening bolsters the theory. In addition to the posterior shifting of Bruch's membrane in medium myopic eyes, there must also be an enlargement of Bruch's membrane opening in particular in highly myopic eyes in which the optic disc (as defined as the area within the peripapillary ring) can be markedly enlarged without showing a nasal overhanging of Bruch's membrane, and in which the gamma zone is also present on the nasal side of the optic disc. The enlargement of the physiologic opening of Bruch's membrane in the optic nerve head of highly myopic eyes can be accompanied by the development of secondary defects of Bruch's membrane in the macular region. Both phenomena point to an increased tension within Bruch's membrane in myopic eyes. It has remained elusive so far, whether an enlargement of the optic nerve head associated opening of Bruch's membrane can release the tension within Bruch's membrane sufficient to reduce the risk of the development of secondary macular Bruch's membrane defects.

In agreement with previous hospital-based studies using conventional fundus photographs, our study showed that both the beta and gamma zones were located most often in the temporal region followed by the inferior region and the superior region, while both zones were most rarely found in the nasal region. The finding of the gamma zone being located more often in the inferior region than in the superior region may be associated with the anatomy of the optic nerve originating in the nasal upper region of the bony orbit, from where the temporal inferior and inferior part of the parapapillary region has the longest distance so that the potential backward pull by the optic nerve may be strongest there. The regional distribution of the gamma zone also fits with the occurrence of peripapillary suprachoroidal cavitations, which are detected in highly myopic eyes with a prevalence of approximately 17% and that are located most often at the temporal inferior and inferior peripapillary region. A peripapillary suprachoroidal cavitation is a localized separation of the peripapillary sclera from the choroid, which is still attached to Bruch's membrane, in a crescent-shaped parapapillary region with orange-yellowish color upon ophthalmoscopy. Bruch's membrane, which in these highly myopic eyes at its end is connected with the structures of the optic nerve head just by the thinned and elongated peripapillary border tissue of the choroid (called Jacoby), would remain in its location, while the sclera, due to its firm connection with the optic nerve at the merging line of the optic nerve dura mater with the peripapillary scleral flange, would be dragged backward by the optic nerve pull. In these highly myopic eyes, the backward pull by the optic nerve would thus not only lead to the development of the gamma zone but also to a separation of the peripapillary sclera from the choroid. Consequently, the occurrence of peripapillary suprachoroidal cavitations are associated with the occurrence of the parapapillary gamma zone (and delta zone), with an optic disc rotation around the vertical disc axis and with high axial myopia.

Future studies may measure prevalence and size of the beta and gamma zones in eyes with glaucomatous optic neuropathy to address the question whether as suggested in pilot studies, the beta zone as compared with the gamma zone was stronger associated with glaucoma than with axial length while in reverse, the gamma zone as compared with the beta zone was stronger associated with axial length than with glaucoma.

Limitations of our study should be discussed. First, as for any population-based study, nonparticipation of eligible individuals might have caused a bias. The participation rate in the Beijing Eye Study was however relatively high 78.8%, and furthermore, the present investigation included only individuals without major eye diseases. Because eye diseases are age-related in their prevalence and because elderly individuals usually show a lower participation rate in a study, focusing the present study on individuals with healthy eyes might only have served to reduce the risk of a participation bias.

In conclusion, in this healthy population, the parapapillary gamma zone was mainly associated with longer axial length and not with age, while a larger beta zone was correlated mainly with older age and to a lower degree with axial length. Both zones were largest in the temporal parapapillary region and smallest in the nasal region. The results may serve to further elucidate the role of the beta zone in the diagnosis of glaucomatous optic neuropathy and the role of the gamma zone for the assessment and pathogenesis of myopic maculopathy.

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