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# Systemic and Ocular Determinants of Peripapillary Retinal Nerve Fiber Layer Thickness Measurements in the European Eye Epidemiology (E3) Population

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***Purpose:*** To investigate systemic and ocular determinants of peripapillary retinal nerve fiber layer thickness (pRNFLT) in the European population.

***Design:*** Cross-sectional meta-analysis.

***Participants:*** A total of 16 084 European adults from 8 cohort studies (mean age range, 56.9±12.3–82.1±4.2 years) of the European Eye Epidemiology (E3) consortium.

***Methods:*** We examined associations with pRNFLT measured by spectral-domain OCT in each study using multivariable linear regression and pooled results using random effects meta-analysis.

***Main Outcome Measures:*** Determinants of pRNFLT.

***Results:*** Mean pRNFLT ranged from 86.8±21.4 μm in the Rotterdam Study I to 104.7±12.5 μm in the Rotterdam Study III. We found the following factors to be associated with reduced pRNFLT: Older age (β = −0.38 μm/year; 95% confidence interval [CI], −0.57 to −0.18), higher intraocular pressure (IOP) (β = −0.36 μm/mmHg; 95% CI, −0.56 to −0.15), visual impairment (β = −5.50 μm; 95% CI, −9.37 to −1.64), and history of systemic hypertension (β = −0.54 μm; 95% CI, −1.01 to −0.07) and stroke (β = −1.94 μm; 95% CI, −3.17 to −0.72). A suggestive, albeit nonsignificant, association was observed for dementia (β = −3.11 μm; 95% CI, −6.22 to 0.01). Higher pRNFLT was associated with more hyperopic spherical equivalent (β = 1.39 μm/diopter; 95% CI, 1.19–1.59) and smoking (β = 1.53 μm; 95% CI, 1.00–2.06 for current smokers compared with never-smokers).

***Conclusions:*** In addition to previously described determinants such as age and refraction, we found that systemic vascular and neurovascular diseases were associated with reduced pRNFLT. These may be of clinical relevance, especially in glaucoma monitoring of patients with newly occurring vascular comorbidities. *Ophthalmology 2018;■:1–12 © 2018 by the American Academy of Ophthalmology*

*Supplemental material available at www.aaojournal.org.*

The assessment of peripapillary retinal nerve fiber layer thickness (pRNFLT) with spectral-domain OCT has become of increasing importance in the evaluation of glaucoma and its progression.[1,2] Although debated, pRNFLT measurements hold promise as a biomarker for neurodegenerative diseases such as Alzheimer's disease and multiple sclerosis.[3,4]

Although pRNFLT measurements have increased insight into the development of diseases, it has been difficult to evaluate which changes fall within the physiologic range. Most OCT devices compare pRNFLT measurements with reference databases that are built into the machine analysis software. These data are mostly derived from relatively small sample populations. Whether these databases adequately capture normal anatomic variation across a wide age range remains unclear.

Few studies have investigated ocular and systemic determinants of pRNFLT in the general population.[5] They reported inconsistent results for many ocular and systemic parameters, including sex and body mass index (BMI).[5,6] To date, only age,[7,8] refraction,[9] and axial length (AL)[10] have been consistently associated with measured pRNFLT across studies. In addition, the majority of large-scale studies assessing these associations were performed in



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young Asian populations.[6,11-14] It is unclear whether these results can be applied to European, that is, mostly white, populations. The purpose of this study was to assess systemic and ocular determinants of pRNFLT using pooled data from 8 European population-based studies.

## Methods

### Included Studies

The European Eye Epidemiology (E3) consortium is a collaborative network of population-based studies across Europe with the overarching aim of developing and analyzing large pooled datasets to increase understanding of eye disease and vision loss.[15] For this study, we analyzed data on pRNFLT from 8 different studies. The included data were cross-sectional, and the right eye was chosen to be the study eye. All studies adhered to the tenets of the Declaration of Helsinki and had local ethical committee approval. All participants gave written informed consent.

### Assessments and Data Analyses

Retinal nerve fiber layer thickness was measured as global pRNFLT with different OCT devices, scan modalities (mostly circular scans), and automated segmentation algorithms in the respective studies (Table 1). The pRNFLT outliers were excluded before analyses according to Chauvenet's criterion.[16] Briefly, depending on sample size, we excluded participants with pRNFLT above or below a certain range of standard deviations from the mean.[16] To investigate the determinants of pRNFLT, multivariable linear regression models including the variables of interest were conducted. Factors to be tested for association with pRNFLT were considered in multiple steps. As the first and most important step, variables were chosen a priori on the basis of literature and availability in the individual studies. Subsequently, we performed univariable linear regression models of potential factors at study level to assess the possible impact on pRNFLT. In the last step, the factors of the multivariable models were decided on as a trade-off between the priority of the respective factors and the maximum possible population size of the model.

The independent variables of the multivariable linear regression model were age, sex, BMI, visual impairment as defined by the World Health Organization (best-corrected visual acuity [BCVA] <0.3 decimal), intraocular pressure (IOP), spherical equivalent (SE), smoking status, and history of systemic hypertension, diabetes, stroke, and dementia. The multivariable regression model was conducted for each individual study, and residuals were then plotted and normal distribution assessed. Because OCT devices were changed within the course of the Rotterdam Study (from 3D-OCT 1000 to 3D-OCT 2000, Topcon Medical Systems, Oakland, NJ), we controlled for the OCT device in the multivariable regression models of the Rotterdam Study II and III. In the TwinsUK Study, we performed a hierarchical multivariable regression model to control for family dependencies between twins (See Study Descriptions and pRNFLT Distributions, available online at www.aaojournal.org).

Subsequently, random-effects meta-analysis was used to combine effect estimates (beta coefficients) of each individual predictor from the multivariable regression models among studies. A random-effects approach was chosen a priori on the basis of the heterogeneity in the data caused by the different OCT devices[17] and the set-up of the studies. Our analyses were conducted twice, with and without patients with known glaucoma.

Not all independent variables of the multivariable regression model were available in every participating study. Therefore, the multivariable regression models in the respective studies were performed without the missing variables, and the study was excluded from the meta-analysis of that respective missing covariate. All analyses were performed with the statistical software RStudio (R version 3.4.1, RStudio Inc., Boston, MA, https://www.rstudio.com/), and statistical significance was set at $P < 0.05$.

## Results

A total of 16 084 participants from 8 population-based studies were included; approximately 1% of pRNFLT outliers per study were excluded (Table S1, available at www.aaojournal.org). The mean age of participants ranged from 56.9±12.3 years in the LIFE Study to 82.1±4.2 years in the Alienor Study. Mean global pRNFLT ranged from 86.8±21.4 μm in the Rotterdam Study I to 104.7±12.5 μm in the Rotterdam Study III (Table 1). Further participant characteristics for each study are presented in Table S1 (available at www.aaojournal.org). The results of the multivariable regression models for each individual study are reported in Table 2. Data on dementia were only available in the Rotterdam Study cohorts and the Alienor Study. Furthermore, in the TwinsUK Study, no sufficient data were available on visual impairment, glaucoma, hypertension, and smoking status; in the LIFE Study, no data were available on visual impairment, SE, and IOP.

In the meta-analyzed multivariable regression model (Table 3 and Fig 1A, B), age and IOP were negatively associated with pRNFLT, even after excluding patients with glaucoma. A history of stroke and hypertension were both associated with a reduced pRNFLT. When substituting hypertension with mean systolic blood pressure (in mmHg), no association was found.

A suggestive, but nonsignificant association with reduced pRNFLT was observed for dementia. Visual impairment as defined by the World Health Organization was associated with reduced pRNFLT in the meta-analysis. We found this association in the Alienor and Rotterdam Study I-III, whereas there was no association in the Montrachet and Coimbra Studies.

Women had a thicker pRNFLT than men did in the meta-analysis. However, when correcting for AL rather than SE in the 5 studies with data on AL, this association disappeared. The SE was positively associated with pRNFLT, even after excluding highly myopic eyes (<−6 diopters) and highly hyperopic eyes (>+4 diopters), as well as eyes with pseudophakia (Fig S1A, B, available at www.aaojournal.org). Longer AL was associated with reduced pRNFLT in our sensitivity analyses ($\beta = -3.48$ μm per mm longer AL, 95% confidence interval [CI], −4.18 to −2.77) (Fig S1C, available at www.aaojournal.org). Both former and current smoking were associated with thicker pRNFLT, but prevalence and associations differed considerably between studies. To assess the influence of education on smoking, we corrected for education, and the associations persisted. After excluding data from the LIFE Study, which is the largest study with the highest proportion of smokers (data weighted >60% in the meta-analysis), the association remained significant for current but not for former smoking (Fig S1D−G, available at www.aaojournal.org). For BMI, we found a small but significant association with increased pRNFLT after excluding patients with glaucoma. All associations except for former smoking held true after excluding the 619 patients with known glaucoma (Table 3). Furthermore, we detected no relevant changes of associations when performing the multivariable regression analyses stratified by sex or when excluding the LIFE study cohort being the largest single study (results not reported).