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► To cite this version:

Monique Breteler, Matthias Mauschitz, Pieter W.M. Bonnemaier, Kersten Diers, Franziska Rauscher, et al.. Systemic and Ocular Determinants of Peripapillary Retinal Nerve Fiber Layer Thickness Measurements in the European Eye Epidemiology (E3) Population. *Ophthalmology: Journal of The American Academy of Ophthalmology*, 2018, 125 (10), pp.1526-1536. 10.1016/j.opthta.2018.03.026 . hal-02341481

HAL Id: hal-02341481

<https://hal.umontpellier.fr/hal-02341481v1>

Submitted on 17 Mar 2024

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Published in:
Ophthalmology

DOI:
[10.1016/j.ophtha.2018.03.026](https://doi.org/10.1016/j.ophtha.2018.03.026)

Publication date:
2018

Document version:
Accepted manuscript

Document license:
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Citation for pulished version (APA):

Mauschitz, M. M., Bonnemaier, P. W. M., Diers, K., Rauscher, F. G., Elze, T., Engel, C., Loeffler, M., Colijn, J. M., Ikram, M. A., Vingerling, J. R., Williams, K. M., Hammond, C. J., Creuzot-Garcher, C., Bron, A. M., Silva, R., Nunes, S., Delcourt, C., Cougnard-Grégoire, A., Holz, F. G., ... European Eye Epidemiology (E3) Consortium (2018). Systemic and Ocular Determinants of Peripapillary Retinal Nerve Fiber Layer Thickness Measurements in the European Eye Epidemiology (E3) Population. *Ophthalmology*, 125(10), 1526–1536. <https://doi.org/10.1016/j.ophtha.2018.03.026>

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Systemic and ocular determinants of peripapillary retinal nerve fiber layer thickness measurements in the E3 population

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35 Medicine, Germany

36

37 **Running head:** Determinants of pRNFLT in the E3 - population

38

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46 **Funding:**

47 The Alienor Study was supported by Laboratoires Théa (Clermont-Ferrand, France);
48 University of Bordeaux (Bordeaux, France); Fondation Voir et Entendre (Paris, France);
49 Caisse Nationale de Solidarité pour l'Autonomie CNSA (CNSA).

50 The Coimbra Study is an Investigator Initiated Study financially supported by Novartis
51 Pharma AG.

52 This publication is supported by the Leipzig Research Centre for Civilization Diseases (LIFE),
53 an organizational unit affiliated to the Medical Faculty of Leipzig University. LIFE is funded by
54 means of the European Union, by the European Regional Development Fund (ERDF) and by
55 funds of the Free State of Saxony within the framework of the excellence initiative (project
56 numbers: 713-241202, 713-241202, 14505/2470, 14575/2470). Dr. Tobias Elze is supported
57 by the following organizations and grants: BrightFocus Foundation, Lions Foundation,
58 Grimshaw-Gudewicz Foundation, Research to Prevent Blindness, and NEI Core Grant
59 P30EYE003790.

60 Montrachet Study: Funding was provided by an Inter-regional grant (PHRC) and the
61 Regional Council of Burgundy. This study was also funded by INRA, CNRS, Université de
62 Bourgogne, Regional Council of Burgundy France (PARI Agrale 1), FEDER (European
63 Funding for Regional Economic Development) and French Government grant managed by
64 the French National Research Agency (ANR) as part of the "Investissements d'Avenir"
65 program (reference ANR-11-LABX-0021-01-LipSTIC Labex).

66 The Rotterdam Study is funded by Erasmus MC and Erasmus University, Rotterdam,
67 Netherlands Organization for the Health Research and Development (ZonMw), the Research
68 Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science,
69 the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the
70 Municipality of Rotterdam. SENSE-COG consortium has received funding from the European
71 Union's Horizon 2020 research and innovation program under grant agreement No 668648.
72 Stichting Lijf en Leven, Krimpen aan de Lek; MD Fonds, Utrecht; Rotterdamse Vereniging
73 Blindenbelangen, Rotterdam; Stichting Oogfonds Nederland, Utrecht; Blindenpenning,
74 Amsterdam; Blindenhulp, The Hague; Algemene Nederlandse Vereniging ter Voorkoming
75 van Blindheid (ANVVB), Doorn; Landelijke Stichting voor Blinden en Slechtzienden, Utrecht;
76 Swart van Essen, Rotterdam; Stichting Winckel-Sweep, Utrecht; Henkes Stichting,
77 Rotterdam; Laméris Ootech BV, Nieuwegein; Medical Workshop, de Meern; Topcon Europe
78 BV, Capelle aan de IJssel, all in The Netherlands, and Heidelberg Engineering, Dossenheim,
79 Germany. Also supported by the NWO Graduate Programme 2010 BOO ([022.002.023](#); HS),

80 the National Institute of Health (Bethesda, MD, USA) Grants R01 EY019112 and R01
81 EY018853, Veterans Administration Grant I01 CX000119, and the Arnold and Mabel
82 Beckman Initiative for Macular Research.

83 TwinsUK phenotyping was funded by the International Glaucoma Association (2013 research
84 award) and the Wellcome Trust. The study also receives support from the National Institute
85 for Health Research (NIHR)-funded BioResource, Clinical Research Facility and Biomedical
86 Research Centre based at Guy's and St Thomas' NHS Foundation Trust in partnership with
87 King's College London.

88 Dr. Robert Finger's research group receives funding from the Else Kröner-Fresenius-Stiftung
89 (GSO/EKFS 16) and the Jackstädt Stiftung.

90
91 **Conflict of interest:** Alain M. Bron reports personal fees from Allergan, personal fees from
92 Bausch Lomb, grants from Horus, personal fees from Théa, personal fees from Carl Zeiss
93 Meditec, outside the submitted work. Catherine Creuzot-Garcher reports grants and personal
94 fees from Allergan, personal fees from Bayer, personal fees and other from Novartis, grants
95 from Horus, grants and personal fees from Thea, outside the submitted work. Cécile Delcourt
96 is consultant for Allergan, Bausch+Lomb, Laboratoires Théa, Novartis and Roche, outside
97 the submitted work. Frank G. Holz reports fees from Heidelberg Engineering, Optos, Zeiss,
98 Genentech, Acucela, Bayer Healthcare and Novartis, outside the submitted work. Robert P.
99 Finger reports fees from Novartis, Bayer, Abbvie, Opthea, Novelion, RetinalImplant and
100 Santen, outside the submitted work. Rufino Silva is member of Advisory Board for Novartis,
101 Bayer, Allergan, Alimera, Alcon, THEA.

102 **Abstract**

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

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

106 **Participants:** 16,084 European adults from eight cohort studies (mean age range from 56.9
107 \pm 12.3 to 82.1 \pm 4.2 years) of the European Eye Epidemiology (E3) consortium.

108 **Methods:** We examined associations with pRNFLT measured by spectral – domain optical
109 coherence tomography in each study using multivariable linear regression and pooled results
110 using random effects meta-analysis.

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

112 **Results:** Mean pRNFLT ranged from 86.8 \pm 21.4 in the Rotterdam Study I to 104.7 \pm 12.5
113 μ m in the Rotterdam Study III. We found the following factors to be associated with reduced
114 pRNFLT: Older age (β =-0.38 μ m/year, 95% confidence interval (CI)=-0.57, -0.18), higher
115 intraocular pressure (IOP; β = -0.36 μ m/mmHg, 95% CI=-0.56, -0.15), visual impairment
116 (β =-5.50 μ m, 95% CI=-9.37, -1.64) and history of systemic hypertension (β =-0.54 μ m, 95%
117 CI=-1.01, -0.07) and stroke (β =-1.94 μ m, 95% CI=-3.17, -0.72). A suggestive, albeit non-
118 significant, association was observed for dementia (β =-3.11 μ m, 95% CI=-6.22, 0.01). Higher
119 pRNFLT was associated with more hyperopic spherical equivalent (SE; β =1.39 μ m/diopter,
120 95% CI=1.19, 1.59) and smoking (β =1.53 μ m, 95% CI=1.00, 2.06 for current smokers
121 compared to never-smokers).

122 **Conclusions:** In addition to previously described determinants such as age and refraction,
123 we found that systemic vascular and neurovascular diseases were associated with reduced
124 pRNFLT. These may be of clinical relevance, especially in glaucoma monitoring of patients
125 with newly occurring vascular co-morbidities.

126 **INTRODUCTION**

127 The assessment of peripapillary retinal nerve fiber layer thickness (pRNFLT) with Spectral –
128 Domain Optical Coherence Tomography (SD-OCT) has become of increasing importance in
129 the evaluation of glaucoma and its progression^{1,2}. Although debated, pRNFLT measurements
130 hold promise as a biomarker for neurodegenerative diseases such as Alzheimer’s disease
131 (AD) and multiple sclerosis (MS)^{3,4}.

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

138 Only few studies investigated ocular and systemic determinants of pRNFLT in the general
139 population⁵. They reported inconsistent results for many ocular and systemic parameters
140 including sex or body-mass-index (BMI)^{5,6}. To date, only age^{7,8}, refraction⁹ or axial length
141 (AL)¹⁰ have been consistently associated with measured pRNFLT across studies. In addition,
142 the majority of large-scale studies assessing these associations were performed in (young)
143 Asian populations^{6,11-14}. It is unclear whether or not these results can be applied to
144 European, i.e. mostly Caucasian, populations.

145 The purpose of this study was to assess systemic and ocular determinants of pRNFLT using
146 pooled data from eight European population-based studies.

147

148 **METHODS**

149 Included studies

150 The European Eye Epidemiology (E3) consortium is a collaborative network of population-
151 based studies across Europe with the overarching aim of developing and analyzing large
152 pooled datasets to increase understanding of eye disease and vision loss¹⁵. For this study,
153 we analyzed data on pRNFLT from eight different studies. The included data were cross-

154 sectional and the right eye was chosen to be the study eye. All studies adhered to the tenets
155 of the Declaration of Helsinki and had local ethical committee approval. All participants gave
156 written informed consent.

157

158 Assessments and data analyses

159 Retinal nerve fiber layer thickness was measured as global pRNFLT with different OCT
160 devices, scan modalities (mostly circular scans) and automated segmentation algorithms in
161 the respective studies (see Table 1). pRNFLT outliers were excluded prior to analyses
162 according to Chauvenet's criterion. Briefly, depending on sample size we excluded
163 participants with pRNFLT above or below a certain range of standard deviations from the
164 mean¹⁶. To investigate determinants of pRNFLT, multivariable linear regression models
165 including the variables of interest were conducted. Factors to be tested for association with
166 pRNFLT were considered in multiple steps. As first and most important step, variables were
167 chosen a priori based on literature and availability in the individual studies. Subsequently, we
168 performed univariable linear regression models of potential factors at study level to assess
169 possible impact on pRNFLT. In the last step the factors of the multivariable models were
170 decided on as a trade-off between priority of the respective factors and the maximum
171 possible population size of the model.

172 The independent variables of the multivariable linear regression model were age, sex, body-
173 mass-index (BMI), visual impairment as defined by the World Health Organization (WHO)
174 (best corrected visual acuity (BCVA) <0.3 decimal), intraocular pressure (IOP), spherical
175 equivalent (SE), smoking status and history of systemic hypertension, diabetes, stroke and
176 dementia. The multivariable regression model was conducted for each individual study and
177 residuals were then plotted and normal distribution assessed. Since OCT devices were
178 changed within the course of the Rotterdam Study (From 3D-OCT 1000 to 3D-OCT 2000,
179 Topcon Medical Systems, Oakland, NJ, USA), we controlled for the OCT device in the
180 multivariable regression models of the Rotterdam Study II and III. In the TwinsUK Study, we

181 performed a hierarchical multivariable regression model to control for family dependencies
182 between twins.

183 Subsequently, random-effects meta-analysis was used to combine effect estimates (beta
184 coefficients) of each individual predictor from the multivariable regression model among
185 studies. A random-effects approach was chosen a priori based on the heterogeneity in the
186 data caused by the different OCT devices¹⁷ and the set-up of the studies. Our analyses were
187 conducted twice, with and without known glaucoma patients.

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

194

195 **RESULTS**

196 A total of 16,084 participants from eight population-based studies were included, about one
197 percent pRNFLT outliers per study were excluded (supplemental Table 1b). The mean age of
198 participants ranged from 56.9 ± 12.3 years in the LIFE Study to 82.1 ± 4.2 years in the
199 Alienor Study. Mean global pRNFLT ranged from 86.8 ± 21.4 microns in the Rotterdam
200 Study I to 104.7 ± 12.5 microns in the Rotterdam Study III (Table 1). Further participant
201 characteristics for each study are presented in supplemental Table 1b. The results of the
202 multivariable regression models for each individual study are reported in Table 2. Data on
203 dementia were only available in the Rotterdam Study cohorts and the Alienor Study.
204 Furthermore, in the TwinsUK Study no sufficient data were available on visual impairment,
205 glaucoma, hypertension and smoking status; in the LIFE Study, no data were available on
206 visual impairment, SE and IOP.

207 In the meta-analyzed multivariable regression model (Table 3 and Figures 1a and 1b), age
208 and IOP were negatively associated with pRNFLT, even after excluding glaucoma patients. A

209 history of stroke and hypertension were both associated with a reduced pRNFLT. When
210 substituting hypertension with mean systolic blood pressure (in mmHg), no association was
211 found.

212 A suggestive, but non-significant association with reduced pRNFLT was observed for
213 dementia. Visual impairment as defined by the WHO was associated with reduced pRNFLT
214 in the meta-analysis. We found this association in the Alienor and Rotterdam Study I-III,
215 while there was no association in the Montrachet and Coimbra Study.

216 Women had a thicker pRNFLT than men in the meta-analysis. However, when correcting for
217 AL rather than SE in the five studies with data on AL, this association disappeared. SE was
218 positively associated with pRNFLT, even after excluding highly myopic (< -6 diopters) and
219 highly hyperopic eyes (> +4 diopters) as well as eyes with pseudophakia (supplemental
220 Figures A and B). Longer AL was associated with reduced pRNFLT in our sensitivity
221 analyses (beta=-3.48 μ m per mm longer AL, 95% CI=-4.18, -2.77) (supplemental Figure C).
222 Both, former and current smoking were associated with thicker pRNFLT, but prevalence and
223 associations differed considerably between studies. To assess the influence of education on
224 smoking, we corrected for education and the associations persisted. After excluding data
225 from the LIFE Study, which is the largest study with the highest proportion of smokers (data
226 weighted >60% in the meta-analysis), the association remained significant for current but not
227 for former smoking (supplemental Figures D-G). For BMI, we found a small but significant
228 association with increased pRNFLT after excluding glaucoma patients. All associations
229 except for former smoking held true after excluding the 619 known glaucoma patients (Table
230 3). Furthermore, we detected no relevant changes of associations when performing the
231 multivariable regression analyses stratified by sex or when excluding the LIFE study cohort
232 being the largest single study (results not reported).

233
234 **DISCUSSION**

235 Our study confirms the previously reported associations of age and SE with pRNFLT and
236 identifies several additional factors associated with pRNFLT, namely IOP (even in individuals

237 without a history of glaucoma), stroke, hypertension and smoking. Furthermore, we found a
238 trend of reduced pRNFLT in participants with dementia. Our results suggest that a number of
239 ocular as well as systemic factors need to be considered when assessing pRNFLT. To date,
240 none of this has for example been implemented as potentially influencing factors in reference
241 databases for OCT devices or any algorithms assessing pRNFLT change.

242 First publications on determinants of OCT – based pRNFLT measurements reported older
243 age and greater AL to be associated with thinner pRNFLT^{18,19}. Budenz and coworkers
244 investigated determinants of pRNFLT in 328 normal subjects aged 18 to 85 years using time
245 domain – optical coherence tomography (TD–OCT) and described a decrease of 2.0 microns
246 pRNFLT per decade and a decrease of 2.2 microns per millimeter AL¹⁹. These estimates are
247 smaller but still compare to our results (decrease of 3.8 microns pRNFLT on average per
248 decade and 3.48 microns per millimeter AL). A subsequent study evaluated determinants of
249 pRNFLT in 542 healthy adults aged 40 to 80 years using SD – OCT (Cirrus HD-OCT; Carl
250 Zeiss Meditec, Inc., Dublin, CA) and confirmed the associations of pRNFLT with age and
251 AL¹¹.

252 Subsequently, larger population studies mostly from Asia were conducted to investigate
253 further determinants of pRNFLT. We have affirmed results from the Beijing Eye Study in
254 2548 participants considering the influence of age and refractive error. That study also
255 showed a higher pRNFLT of 2.9 microns in women¹⁴, in keeping with our results of women
256 having a higher pRNFLT of 2.2 microns. Similar to our models, the Beijing Eye Study
257 corrected for refractive error instead of actual AL. Interestingly, after correcting for AL in our
258 analyses, sex was no longer associated with pRNFLT. Based on this, we hypothesize that
259 AL, which is on average shorter in women, confounds the effect of sex on pRNFLT. In
260 general, SE is a good proxy for AL and we found a strong association of higher SE with
261 thicker pRNFLT, even in both our sensitivity analyses, which eliminated subjects with high
262 refractive errors. The underlying mechanisms of the association of longer AL and thinner
263 pRNFLT are arguable²⁰. Frequently suggested mechanisms are either a stretching due to a
264 longer eye bulb or artificially decreased measurements due to magnification^{21,22}. However,

265 irrespective of the causal mechanism, the clinical relevance of adjusting for refraction or AL
266 in OCT – imaging seems obvious.

267 Higher IOP was associated with reduced pRNFLT in our analyses even after excluding
268 known glaucoma patients. However, since glaucoma was self-reported in some of the
269 participating studies, not all actual glaucoma patients might have been excluded in our
270 analyses. Visual impairment (BCVA < 0.3 decimal) as a proxy for any ocular pathology was
271 associated with thinner pRNFLT in the Alienor Study and all of the Rotterdam Studies. The
272 Coimbra and Montrachet Study were likely underpowered to find an effect, because of very
273 few cases with reduced BCVA in these studies.

274 Previous studies reported contradictory results on the impact of hypertension and blood
275 pressure on pRNFLT^{9,23,24}. Our results show reduced pRNFLT in hypertensive patients, but
276 no association of pRNFLT with actual systolic blood pressure. Blood pressure
277 measurements, however, are known to vary with method and associations with systolic blood
278 pressure may have been masked by any use of antihypertensive medication. In contrast to
279 hypertension, most studies investigating the effect of diabetes on pRNFLT report diabetic
280 patients to have thinner pRNFLT^{25,26}. This is in not agreement with our results that do not
281 show an association of reduced pRNFLT in diabetic patients. Nether the less, we
282 hypothesize that microvascular pathology and ischemia due to hypertension and/or diabetes
283 may be a cause for reduced pRNFLT, as it has been suggested previously²⁵.

284 Both, former and current smoking were associated with thicker pRNFLT in our meta-analysis,
285 even in several sensitivity analyses including correction for educational level. This
286 association does not seem biologically plausible given the observed pRNFLT decrease in
287 metabolic diseases. Potential biologic explanations could be reduced axonal flow or axonal
288 swelling in the course of axonal degeneration due to intake of neurotoxins and cytotoxins
289 from cigarette smoke. However, our results are in contrast with findings of earlier studies^{27,28},
290 which reported reduced pRNFLT in smokers. Suggested mechanisms leading to decreased
291 pRNFLT were toxic damage through free radicals, increased IOP and reduced perfusion²⁷⁻²⁹.
292 We controlled for IOP as well as hypertension and diabetes, which all may influence

293 perfusion. It is therefore unclear what might explain this association. Current smokers were
294 on average younger in our participating studies compared to never and former smokers.
295 Hence, even though we controlled for age in our models, we cannot entirely rule out residual
296 confounding. Additionally, the E3 studies are not representative studies of European
297 populations and smoking percentages therefore do not reflect actual percentages. There was
298 heterogeneity between studies considering smoking prevalence and oppositional effects of
299 former smoking in some studies. After excluding the LIFE Study, which was dominantly
300 weighted in the smoking meta-analysis, the Rotterdam Study III showed to be weighted
301 strongest for current smoking. When excluding also the Rotterdam Study III, the impact of
302 smoking is weakened but holds true. Still, the associations seem to be particularly driven by
303 the large studies. This is also underlined by increasing heterogeneity for former and current
304 smoking in the meta-analysis after excluding the LIFE Study. Moreover, there is no
305 information on the time interval between cessation of smoking and OCT – imaging for the
306 former smokers, which may have an impact, as well. Further studies are needed to confirm
307 or refute our observation, which may well be a chance finding.

308 Past studies have reported stroke patients to have thinner pRNFLT, which was hypothesized
309 to be caused by transneuronal retrograde degeneration^{30,31}. Our data confirm the association
310 of stroke and decreased pRNFLT. Additionally, in dementia patients we found a trend of
311 reduced pRNFLT. Again, this is in accordance to various previous studies, which report
312 dementia patients to have reduced pRNFLT^{4,32}. Thus far, the underlying mechanisms remain
313 unclear. Loss of peripapillary RNFL is a hallmark of glaucoma and longitudinal pRNFLT
314 evaluation is a crucial part of glaucoma management. In our meta-analysis, all associations
315 persisted after excluding known glaucoma patients except for former smoking. This indicates
316 that the detected determinants are independent of the presence of glaucoma.

317 As described previously, structural decline of pRNFLT occurs before functional loss in
318 perimetry in glaucoma patients. An earlier study reported the difference in pRNFLT between
319 glaucomatous and healthy eyes eight years before the onset of visual field impairment to be
320 around 5 μm ³³. This is in the range of some associations found in our study and underlines

321 the potential impact on the interpretation of pRNFLT. Our results have two main clinical
322 implications. Firstly, the normative databases built into the devices should reflect our results,
323 when presenting normal values for pRNFLT. Also, presence of vascular disease including a
324 history of stroke should be considered when defining normative datasets or when clinically
325 evaluating pRNFLT. As discussed above, the magnitude of impact of the respective
326 determinants may have clinical relevance, especially in the presence of more than one factor
327 reducing pRNFLT. Secondly, in glaucoma or other patients followed up with pRNFLT
328 measurements, an incident stroke or dementia may cause a decrease in pRNFLT, which
329 would not primarily be due to glaucoma or other ocular disease progression. For example,
330 this may simulate an aggravation of glaucoma and needs to be considered by the clinician
331 when tailoring the glaucoma management.

332 The strengths of this study consist of the large pooled sample combining data of eight
333 studies from five European countries. To our knowledge, this study represents the largest
334 European study on determinants of pRNFLT thus far. As mentioned, previous population
335 studies reporting data on associations with pRNFLT were conducted in mostly Asian
336 populations and results cannot directly be transferred to European individuals. The
337 associations of this study were assessed in meta-analyses of all participating populations,
338 thus they are not limited to one single population only. This reduces the possibility that an
339 association was solely due to chance within one population and increases generalizability.
340 However, several limitations of our study need to be considered. The use of different OCT–
341 devices between studies may have increased variability and prohibited direct pooling of
342 pRNFLT data. To overcome this lack of direct comparability we performed the analysis
343 separately within studies and then pooled studies' effect estimates using random-effect
344 meta-analysis. Furthermore, we found no interactions between type of device and any
345 predictor variable in additional sensitivity analyses in the Rotterdam Study II and III, which
346 had a device upgrade within course of the study. However, residual influence of different
347 OCT devices cannot be entirely excluded. As expected when combining different large- scale
348 population studies, we observed between study heterogeneity for the independent variables

349 and their influence on pRNFLT. The degree of heterogeneity of the respective covariates
350 was assessed using the I² – statistics and ranged from 0% to 97% (see Table 3). As
351 described, this heterogeneity between studies was addressed by using random effect meta-
352 analysis¹⁷. In accordance with previous literature, the relationship between pRNFLT and age
353 was linear in our sample. Having no data for children and young adults, we do not know
354 whether the relationship between pRNFLT and age is strictly linear throughout life but would
355 assume so based on our data. Thus, we investigated associations using multivariable linear
356 regression modeling. Based on this, any non-linear relationships may have been
357 underrepresented. Quality control was performed within each study differently (supplemental
358 Table 2). Some studies performed manual (re)-segmentation, excluded OCT images below a
359 certain scan quality and scans with artifacts, while others included all scans with sufficient
360 quality as evaluated by the performing technician. As sensitivity analysis we excluded
361 participants with an image quality value below 45 (as recommended by the manufacturer) in
362 the Rotterdam Studies I-III. We found no relevant changes of direction in any association, but
363 the confidence intervals became broader due to a reduced sample size (supplemental Table
364 3). Hence, even though the lack of centralized quality control is a limitation to our analyses,
365 the impact of poor quality scans seems to be low as indicated by our supplemental sensitivity
366 analyses. Within each study, the number of participants in which OCT imaging could not be
367 performed or in which the images were of low quality and thus unusable is a small proportion
368 only (supplemental Table 2). For example, in the Rotterdam Study I-III the number of
369 participants with no or insufficient OCT data was 10%, 6% and 15%, respectively. These
370 subjects were older and more likely to have stroke (RS I), dementia (RS II and III) and
371 hypertension (RS III) than the included participants. This indicates that our associations may
372 be underestimations of the true effect. Several independent variables were not available in
373 some studies. Therefore not all multivariable models could be corrected for all variables.
374 However, no relevant differences of associations were detectable, when comparing studies
375 with and studies without any missing data. Hence, the absence of certain variables in some
376 studies did not relevantly alter the associations of the available data. Methods of

377 assessments varied between our studies. This concerns e.g. the best-corrected visual acuity,
378 which was sometimes measured subjectively and sometimes by autorefractor. In addition,
379 information on diseases was assessed differently. While glaucoma was defined based on
380 optic disc evaluation and perimetry in the Alienor Study and Rotterdam Study I-III, it was self-
381 reported in the LIFE Study. Furthermore, we did not distinguish between the various types of
382 dementia, which may have different impact on pRNFLT. These differences contribute again
383 to larger heterogeneity and the relation between self-reported diseases and pRNFLT may
384 have been estimated with less precision. Lastly, our data were cross-sectional only, thus
385 causal deductions from the detected associations are limited and further longitudinal studies
386 are needed.

387 In conclusion, the current analyses identified important additional determinants of pRNFLT,
388 which should be considered when assessing pRNFLT both clinically and in epidemiological
389 research. The magnitude of changes in pRNFLT by determinant is likely clinically relevant
390 and the biology of pRNFLT thinning is complex, with mechanical pressure, microvascular
391 ischemia and neuronal degeneration being implied. This is reflected in the complexity of
392 factors, which influence pRNFLT and hence need to be considered. In particular, the
393 associations with systemic vascular and neurovascular diseases merit further research.

394 **Acknowledgments**

395 The authors would like to gratefully acknowledge the contribution of the following persons:

396 Alberta A. H. J. Thiadens (Rotterdam), Nomdo M. Jansonius (Groningen/Rotterdam) and

397 Paulus de Jong (Rotterdam). The authors would additionally like to thank Dr Matthias

398 Nuechter (LIFE) for his enthusiastic assistance to this collaborative research, Dr. Kerstin

399 Wirkner (LIFE) and her team for data acquisition, and Dr. Toralf Kirsten (LIFE) for IT

400 structure and overall support. Furthermore, the authors express sincere thanks to Verena

401 Brendler (LIFE) and Yvonne Dietz (LIFE) for data management.

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Figure legends

Figure 1a: Forest plots of meta-analyzed associations with pRNFLT from multivariable regression models (Age, sex, spherical equivalent, intraocular pressure and visual impairment). The beta-coefficients [95% Confidence Interval] show the influence of each parameter on pRNFLT within the respective study, the percentage represents the mathematically determined weighting of each study within the meta-analysis.

Figure 1b: Forest plots of meta-analyzed associations with pRNFLT from multivariable regression models (Smoking, hypertension, stroke and dementia). The beta-coefficients [95% Confidence Interval] show the influence of each parameter on pRNFLT within the respective study, the percentage represents the mathematically determined weighting of each study within the meta-analysis.