Diagnostic Performance of Peripapillary Retinal Nerve Fiber Layer Thickness for Detection of Glaucoma in an Elderly Population: The ALIENOR Study

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Purpose. To assess diagnostic accuracy of spectral-domain optical coherence tomography (SD-OCT) to discriminate glaucoma and control subjects in an elderly population.

Methods. The antioxidants, essential lipids, nutrition and ocular maladies study (ALIENOR: "Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires") is a population-based study. From 2009 to 2010, a total of 624 subjects, aged 74 years or older underwent a complete eye examination, including optic disc color photography and SD-OCT examination of the macula and the optic nerve head. Glaucoma diagnosis was made using retinophotography of the optic nerve head and International Society for Epidemiologic and Geographical Ophthalmology criteria. Average and sectorial peripapillary retinal nerve fiber layer thicknesses (RNFLT) were compared between glaucoma and control subjects using area under the receiver operating characteristic curves (AUC), positive and negative likelihood ratios (LR+/LR−), and diagnostic odds ratios (DOR).

Results. A total of 532 subjects had complete data, 492 were classified as controls and 40 were classified as glaucoma. Mean age was 82.1 ± 4.2 years and average RNFLT was significantly different between both groups (controls: 88.7 ± 12.2 μm, glaucoma: 65.4 ± 14.4 μm, $P < 0.001$). Highest AUC values were observed for average (0.895), temporal-inferior (0.874), and temporal-superior (0.868) RNFLT. Temporal-superior RNFLT had the highest DOR (25.31; LR+, 4.65; LR−, 0.18), followed by average RNFLT (DOR: 24.80; LR+, 6.36; LR−, 0.26). When using the normative database provided by the machine, DOR increased to 31.03 (LR+, 1.75; LR−, 0.06) if at least one parameter was considered abnormal (at $P < 0.05$).

Conclusions. Parameters of SD-OCT RNFL may provide valuable information in a screening strategy to improve glaucoma detection in a general population of elderly people.

Keywords: optical coherence tomography, OCT, spectral-domain OCT, glaucoma screening, aging, likelihood ratios

Glaucoma remains the most frequent cause of irreversible blindness worldwide by affecting more than 60.5 million people in 2010 and with an estimated increasing prevalence up to 111.8 million in 2040.[1,2] The incidence of glaucoma is strongly associated with increasing age and this estimate mainly results from an expected increase in life expectancy and a higher rate of elderly people within general populations.[3–6] As visual impairment and blindness are important determinants in quality of life—particularly in elderly people with a reported higher dependence in activities of daily living (ADL score) and a higher risk of mortality—the socioeconomic burden of glaucoma is recognized as an important and increasing health problem that will require public care strategy to preserve visual function and wellbeing in such populations.[7–10]

Although glaucoma is defined as a chronic optic neuropathy, the accuracy of optic disc photography—interpreted by either glaucoma experts or a representative panel of ophthalmologists for diagnosing glaucoma or even glaucomatous change—is in general moderate, and machine classifiers may outperform most observers.[11–13] By contrast, spectral-domain optical coherence tomography (SD-OCT) is a noninvasive technology, widely used by ophthalmologists in current practice. It enables fast high-resolution cross-sectional imaging of tissue morphology and also provides objective, quantitative, and reproducible measurements of peripapillary retinal nerve fiber layer (RNFL) thickness with an axial resolution of 5 μm.[14,15] By accurately measuring optic nerve head parameters, this technology may be a worthwhile test to screen for glaucoma. Numerous case-control studies have already shown good diagnostic performances of SD-OCT to detect glaucoma.[16–29] However, only very few studies have been performed in a population setting.[30–32] In a systematic review of studies on imaging technology for diagnosing glaucoma, Michelessi et al.[33] highlighted high risk of bias in these case-control studies, mainly related to patient selection as defined by the QUADAS 2 quality assessment tool, and raised concerns about the applicability of these results in

clinical practice. Indeed, case-control studies are essential to provide initial diagnostic performances of a test, but it has also been demonstrated that this type of study design can overestimate results mainly by an inappropriate selection of cases and controls, thus making results not applicable for screening purpose in a general population.[34] Interestingly, Springelkamp et al.[30] observed good discriminating performances of the macular region parameters in a population-based study, in which one eye was randomly selected for analysis. Moreover, Li et al.[32] demonstrated that time-domain OCT imaging technology performed in high-risk populations—defined by either a family history of glaucoma or self-described Caribbean origin—may be useful to screen the disease, and worthwhile for decision makers to define an appropriate screening strategy by targeting these high-risk populations.[30,32]

Whereas glaucoma prevalence is rapidly increasing with increasing age, and the ability of SD-OCT to discriminate glaucoma has been validated in case-control studies, little is known on the ability of this imaging technology to screen the disease in elderly people and, to our knowledge, no population-based studies have specifically focused on this population subgroup more likely to have the disease and visual-related impairment in quality of life. Furthermore, as all stages of AMD are frequent in elderly people with a prevalence of early and late AMD that can reach 29.7% and 7.1%, respectively, for people aged older than 75 years and 37.1% to 30.8% for people aged older than 80 years,[35–38] SD-OCT measurements of retinal ganglion cell thickness may be at least partly affected by these abnormalities, thus making this parameter no longer clinically applicable in a screening strategy for glaucoma in such populations.

We therefore investigated the ability of SD-OCT peripapillary RNFL parameters to screen for glaucoma in a population-based study of elderly people.

Materials and Methods

The antioxidants, essential lipids, nutrition and ocular maladies study (ALIENOR: "Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires") is a prospective population-based epidemiologic study on age-related eye diseases performed at the University Hospital of Bordeaux. The complete methodology of this study was published previously.[39,40]

Study Population

The aim of the ALIENOR study was to assess the associations of age-related eye diseases with nutritional factors and take into account other major determinants of eye diseases, including gene polymorphisms, and environmental and vascular factors.[39] Subjects of the ALIENOR Study were recruited from an ongoing population-based study on the vascular risk factors for dementia, the Three-City (3C) study.[40] The 3C study included 9294 subjects aged 65 years or older from three French cities (Bordeaux, Dijon, and Montpellier), 2104 of whom were randomly recruited in Bordeaux. Subjects were contacted individually from electoral rolls. They were initially recruited from 1999 to 2001 and followed-up approximately every 2 years thereafter.

The study ALIENOR consists of eye examinations offered to all participants of the 3C cohort in Bordeaux since the third follow-up (2006–2008). Among the 1450 participants reexamined between October 2006 and May 2008, a total of 963 (66.4%) participated in the ALIENOR study's baseline eye examination. This examination consisted in the evaluation of age-related eye-diseases: AMD, glaucoma, cataract, and dry eye syndrome. Detailed characteristics of participants and nonparticipants have been published elsewhere.[39]

At the fourth follow-up (2009–2010), SD-OCT examinations were added to the eye examinations. Among the 963 participants, 624 (59 deaths, 265 refusals, 15 relocated) participated in the ALIENOR study's second eye examination, the target of the present study. They were aged 74 years or older. At this follow-up, representativeness of our population sample were tested using the database of the National Institute for Statistics and Economics Studies INSEE (Institut National de la Statistique et des Etudes Economiques) for the Bordeaux area. There was no significant difference in age or sex distribution, residency location, and loneliness index between our population sample and data of the Bordeaux area population.

This research followed the tenets of the Declaration of Helsinki. Participants gave written consent for participating in the study. The design of the ALIENOR study was approved by the ethical committee of Bordeaux (Comité de Protection des Personnes Sud-Ouest et Outre-Mer III) in May 2006.

Eye Examination

Each subject underwent an ophthalmologic examination that included a best-corrected visual acuity measurement; an intraocular pressure measurement by a noncontact tonometer (KT 800; Kowa, Tokyo, Japan); macular and optic disc color photography by nonmydriatic retinophotograph (TRC NW6S; Topcon, Inc., Tokyo, Japan); an SD-OCT examination (Spectralis, software version 5.4.7.0; Heidelberg Engineering, Heidelberg, Germany); a break-up time test; and a central corneal thickness measurement (Pachpen; Accutome, Inc., Malverne, PA, USA), after local anesthesia with oxybuprocaine eye drops. Data collection was planned before performing all ophthalmologic examinations. The use of eye drops was refused by 63 (12.7%) of the participants, because of previous allergy to eye drops, or other contraindications.

Retinal photographs were interpreted in duplicate by two specially trained technicians masked for clinical information and ophthalmologic examination results of participants including SD-OCT RNFL thickness parameters. Inconsistencies between the two interpretations were adjudicated by a glaucoma specialist for classification of glaucoma and by a retina specialist for classification of AMD or other retinal diseases. All cases of glaucoma and retinal disease were reviewed and confirmed by specialists.

Classification of Glaucoma

Glaucoma classification was performed at the end of the fourth follow-up and glaucoma specialist was masked for SD-OCT measurements performed during the follow-up. Glaucoma was classified according to the classification proposed by Foster et al.,[41] using two steps, as previously detailed.[39] First, the vertical cup/disc ratio (VCDR) and the minimal rim/disc ratio were estimated from optic disc photographs. Participants were classified as suspects for glaucoma when, in at least one eye, VCDR was $\geq$0.65, minimal rim/disc ratio was $\leq$0.1, or when an asymmetry of VCDR between eyes of $\geq$0.2 was observed. For glaucoma suspect cases, an additional eye examination was performed by a glaucoma specialist including a white-on-white visual field test (Octopus 101; Haag-Streit, Koniz, Switzerland), an examination of the optic disc by slit-lamp and of the iridocorneal angle by gonioscopy, and an intraocular pressure (IOP) measurement.

Glaucoma was defined according to three levels of evidence. In category 1, diagnosis was based on structural evidence (VCDR on optic nerve photographs $\geq$0.7 and/or

asymmetry of VCDR >0.2 and/or minimal rim: disc ratio ≤0.1) associated with functional evidence (visual field showing at least three contiguous nonedge points with corrected $P < 1\%$, of which at least 1 point is with corrected $P < 0.5\%$), in the absence of other disease (in particular vascular) that might explain the findings. Category 2 was based on advanced structural damage (VCDR ≥0.8 or asymmetry of VCDR >0.3) with unproven field loss (unfeasible or unreliable visual field examination). Category 3 included subjects with very low vision (visual acuity <3/60) for whom optic disc photographs and visual field could not be obtained, but glaucoma diagnosis was confirmed by their treating ophthalmologist. All glaucoma cases were classified according to category 1 criteria, except one case with category 2 criteria, and one case with category 3 criteria. The final classification was reviewed and confirmed by a glaucoma specialist. All cases of glaucoma were classified as open angle glaucoma (OAG).

SD-OCT Measurements

All images were acquired and reviewed by specially trained technicians to control quality of the signal strength and accurate centration and segmentation of the RNFL circle scan acquisition. Glaucoma classification was performed at the end of the fourth follow-up. Therefore, technicians were masked for glaucoma diagnosis and for clinical information or examination, including optic disc photography analysis, when SD-OCT measurements were performed. Thickness measurements of RNFL were obtained using the high-resolution protocol and calculated using the circle scan provided by the machine, which consisted of a 3.45-mm diameter circle scan centered on the optic disc. The standard mean keratometry value of 7.7 mm of the ophthalmic software and device (Heidelberg Eye Explorer; Heidelberg Engineering) was applied for SD-OCT measurements. Thickness measurements of RNFL were obtained using 1536 A-scans of low coherence near-infrared (840 nm) light beam. Correction for fovea-disc orientation is incorporated in the software and a real-time eye tracking system is used to compensate for eye movements. To increase image quality, multiple frames are gathered and averaged for noise reduction and to generate peripapillary RNFL curve. Global and sectorial (nasal and temporal quadrants, temporal-superior, nasal-superior, temporal-superior and nasal-inferior sectors) peripapillary RNFL thicknesses were automatically segmented and calculated. All examinations were checked for segmentation errors and, in case of imprecise retinal layer segmentation on the raw image, inner and outer boundaries of the peripapillary RNFL were manually corrected. For each RNFL parameter, the software (Heidelberg Engineering) provides a classification (within normal, measured value within 95% of normal distribution; borderline, measured value between 95% and 99% of normal distribution; and outside normal limits, measured value below 99% of normal distribution) based on the age-matched comparison with an internal normative database of 201 healthy eyes of Caucasian patients. Signal strength lower than 15 dB (range, 0–40) or acquisitions with artifacts were excluded from the analysis. When both eyes of a participant had complete data, we analyzed the most affected eye defined by the lowest average RNFL thickness between the two eyes.

Statistical Analysis

For continuous variables, results were presented using means ± standard deviations and for categorical variables; results were presented using n and percentage.

For both groups, normality assumption was assessed using a visual inspection of the distribution with a Gaussian shape of data and symmetry of distribution with the median line. Furthermore, even though the sample size of the glaucoma group is larger than 30, the normal distribution of data was also evaluated using a Kolmogorov-Smirnov test.

Comparisons between control and glaucoma subjects were examined with χ^2 test and Student's t-test, as appropriate. For the latter test, homogeneity of variances was systematically evaluated and in case of heterogeneity of variances an appropriate Welch test was performed.

Additionally, a nonresponder analysis was performed between included (responders) and nonincluded (nonresponders) participants to compare demographic characteristics between the two groups and to assess potential nonresponders bias in the final statistical analysis.

Specificity, sensitivity, positive predictive value, and negative predictive value of different quadrant RNFL to detect glaucoma were determined. The areas under the receiver operating characteristic curves (AUC) were calculated. The best cutoff values were established as the ones with higher result of the sum of sensitivity and specificity (Youden's index). The Youden's index gives equal weight to sensitivity and specificity and the cutoff maximizing the Youden's index minimizes the total number of misclassified subjects (false positives and false negatives).

Likelihood ratios (LRs) were computed for positive (the odds that a positive result would be expected from a subject with glaucoma compared with control) or negative (the odds that a negative result would be expected from a subject with glaucoma compared with control) test results. Likelihood ratios can be directly incorporated into the calculation of posttest probability of disease by using the formulation of the Bayes theorem. Likelihood ratios express how much a test result raises or lowers the pretest odds of a disease with a value of one meaning that the test result does not provide additional information. Likelihood ratios greater than 10 or less than 0.1 are associated with a strong influence on posttest probability, LRs from 5 to 10 or from 0.1 to 0.2 are associated with a moderate influence and LRs from 2 to 5 or from 0.2 to 0.5 are associated with a small influence.[42] Finally, the diagnostic odds ratio (DOR) of a test, as an additional indicator of diagnostic accuracy, is the ratio of the odds of positivity in disease relative to the odds of positivity in nondisease. It can easily be calculated as the ratio of positive to negative likelihood ratios. The value of DOR ranges from 0 to infinity with higher values indicating better discriminating performances.[43]

All statistical analyses were performed using statistical software (SAS, version 9.2 SAS Institute, Inc., Cary, NC, USA).

Results

Demographic Characteristics

A total of 624 participants were evaluated in the second follow-up of the ALIENOR study. We excluded 92 participants from the analysis: 18 were not diagnosed with glaucoma due to poor quality of the retinophotography and optic disc measurements could not be performed; 26 had missing SD-OCT examinations; and 48 had poor signal strength or SD-OCT examination artifacts. Finally, 532 participants had complete data and were included for analysis.

Table 1 shows comparison of demographic characteristics between included and nonincluded participants. There was no significant difference in the distribution of sex or mean age, refractive error spherical equivalent (SE), IOP, and VCDR between the two groups. Prevalence of glaucoma was similar in the two groups ($P = 0.28$).

Table 1. Demographic Characteristics Between Included and Nonincluded Participants

Characteristics	Total (n = 624)	Included Participants (n = 532)	Nonincluded Participants (n = 92)	P Value
Age, years (SD)	82.2 (4.3)	82.1 (4.2)	82.6 (4.4)	0.26
Male subjects, n (%)	233 (33.6)	206 (38.7)	27 (29.3)	0.09
Glaucoma, n (%)	43 (7.1)	40 (7.5)	3 (4.1)	0.28
Mean SE, D	0.70 (2.02)	0.79 (1.52)	0.06 (4.02)	0.12*
VCDR, SD	0.46 (0.10)	0.46 (0.09)	0.46 (0.11)	0.99
Minimal rim ratio, SD	0.19 (0.05)	0.19 (0.04)	0.19 (0.05)	0.75
IOP, mm Hg (SD)	14.34 (2.52)	14.24 (2.35)	14.88 (3.32)	0.08*

D, diopters.
* Welch test (heterogeneity of variances).

A total of 492 subjects were included in the control group and 40 subjects in the glaucoma group. The prevalence of glaucoma was 7.5% (95% confidence interval: 5.3; 9.8). The mean age was 82.1 ± 4.2 years and was not significantly different between subjects with and without glaucoma (Table 2). Other demographic characteristics such as sex, mean IOP, and mean refractive error spherical equivalent were not significantly different between the two groups.

As expected, VCDR was significantly higher and minimal rim ratio was significantly thinner ($P < 0.001$) in subjects with glaucoma. Additionally, mean deviation (MD) of the visual field test was 8.73 ± 4.82 dB (0.6–22.7 dB) in subjects with glaucoma. We found 50% ($n = 19$) had a moderate glaucoma with MD values ranging from 6 to 12 dB, 15.8% ($n = 6$) had MD value lower than 6 dB and 34.2% ($n = 13$) had an advanced glaucoma with MD values ≥12 dB.

Comparison of RNFL Thickness Measurements Between Glaucoma and Control Groups

Mean global RNFL thickness was 88.7 ± 12.2 μm in the control group and was 65.4 ± 14.4 μm in the glaucoma group ($P < 0.001$). As shown in Table 3, each sectorial RNFL thickness measurement was significantly lower in subjects with glaucoma ($P < 0.001$).

Table 4 shows AUC curves and optimal sensitivity, specificity, predictive values, and likelihood ratios for all RNFL parameters. The highest AUC curve value was observed for the average RNFL thickness parameter (0.895) with best performances observed at 75 μm (sensitivity, 77.5%; specificity, 87.8%; positive predictive value, 34.1%; and negative predictive value, 98.0%). Temporal-inferior and temporal-superior RNFL thickness parameter had AUC values of 0.874 and 0.868, respectively. All thickness parameters had very high negative predictive values ranging from 96.4% for the temporal quadrant to 99.0% for the nasal-inferior sector.

Additionally, negative (–) and positive (+) LRs of OCT parameters had a moderate effect for influencing posttest probability. Lowest LR– values were observed for the nasal-inferior sector (0.13) and the nasal quadrant (0.17), whereas highest LR+ values were observed for the average RNFL parameter (6.36) followed by temporal-superior (4.65) and temporal-inferior (4.36) sectorial parameters. Finally, when calculating DOR, temporal-superior sectorial RNFL and average RNFL parameters had comparable high diagnostic performances for discriminating glaucoma and control groups with highest DOR values of 25.31 and 24.80, respectively. Indeed, for average RNFL, LR+ value indicates that a glaucoma subject has a 6.36-fold odds of having an average RNFL lower than 75 μm (positive test), compared with a subject without glaucoma, while the LR– value indicates that a glaucoma subject has a 0.13-fold odds (i.e., 7.69-fold lower odds) of having an average RNFL greater than 75 μm (negative test). The diagnostic odds ratio of 24.8 indicates that the odds of having an average RNFL greater than 75 μm is 24.8-fold higher in subjects without than with glaucoma.

Performance of Spectralis SD-OCT for Detection of Glaucoma Using Abnormal Measurements Provided by the Machine

Table 5 shows the ability of the SD-OCT device (Heidelberg Engineering) to screen for glaucoma using statistically abnormal measurements of the RNFL analysis printout provided by the machine and the internal normative database.

Temporal-inferior and temporal-superior sectorial RNFL parameters had the highest sensitivity values (temporal-inferior: cutoff P value at 5%, 85.0% and cutoff P value at 1%, 77.5%; temporal-superior: cutoff P value at 5%, 85.0% and cutoff P value at 1%, 77.5%) followed by average RNFL parameter (cutoff P value at 5%, 82.5% and cutoff P value at 1%, 77.5%). Specificity values ranged from 73.2% for the 5% cutoff P value of the temporal-inferior sectorial parameter to 97.0% for the 1% cutoff P value of temporal quadrant parameter. Negative predictive values were particularly high with values ranging from 93.2% (1% cutoff P value of the nasal-

Table 2. Demographic Characteristics Between Control and Glaucoma Groups

Characteristics	Total (n = 532)	Control Group (n = 492)	Glaucoma Group (n = 40)	P Value
Age, y (SD)	82.1 (4.2)	82.0 (4.2)	82.8 (4.3)	0.27
Male subjects, n (%)	206 (38.7)	188 (38.2)	18 (45.0)	0.40
Mean SE, D	0.79 (1.52)	0.82 (1.54)	0.44 (1.23)	0.13
VCDR, (SD)	0.46 (0.09)	0.44 (0.07)	0.65 (0.11)	<0.0001*
Minimal rim ratio, (SD)	0.19 (0.04)	0.20 (0.04)	0.11 (0.05)	<0.0001
IOP, mmHg (SD)	14.24 (2.35)	14.2 (2.3)	14.4 (3.0)	0.64*
MD of the visual field test, dB (SD)	NA	NA	8.73 (4.82)	NA

* Welch test (heterogeneity of variances).

Table 3. Mean Peripapillary RNFL Thickness Measurements Between Control and Glaucoma Groups

RNFL Thickness, µm Mean (SD)	Control Group (n = 492)	Glaucoma Group (n = 40)	P Value
Average	88.7 (12.2)	65.4 (14.4)	<0.0001
Quadrant			
Temporal	65.0 (12.5)	53.2 (16.2)	<0.0001*
Nasal	65.4 (14.2)	51.8 (14.3)	<0.0001
Sectorial			
TS	114.9 (21.3)	79.6 (23.3)	<0.0001
TI	121.3 (22.6)	77.4 (29.6)	<0.0001
NS	90.2 (21.7)	67.4 (18.0)	<0.0001
NI	96.0 (22.0)	72.8 (17.6)	<0.0001

NI, nasal-inferior; NS, nasal-superior; TI, temporal-inferior; TS, temporal-superior.

* Welch test (heterogeneity of variances).

inferior sector) to 98.4% (5% cutoff P value of the temporal-superior and -inferior sectors).

Positive LRs ranged from 2.48 for the 5% cutoff P value of the nasal-superior RNFL thickness to a stronger influence for influencing posttest probability of 9.02 for the 1% cutoff P value of the temporal quadrant RNFL thickness. The lowest LR– value was 0.20 for the 5% cutoff P value of the temporal-inferior sectorial RNFL thickness, followed by the 5% cutoff P value of the average RNFL thickness (LR–, 0.23). We also observed DOR of 24.80 and 21.85 for the 1% cutoff P value of average RNFL and temporal-superior sectorial RNFL thicknesses, respectively.

Finally, when combining all RNFL parameters, we observed a stronger effect of LR– for influencing posttest probability, with lower LR– value of 0.06 if at least one parameter had a cutoff P value $\leq$ 5% and an LR– value of 0.14 if at least one parameter had a cutoff P value $\leq$1%. The diagnostic odds ratio value was 23.32 if at least one parameter had a cutoff P value $\leq$1%, it improved to 31.03 if at least one parameter had a cutoff P value $\leq$5%. These values indicate that, compared with subjects without glaucoma, a subject with glaucoma had 0.14-fold odds (i.e., 7.14-fold lower odds) of having all RNFL thickness parameters considered normal or borderline by the normative database and 0.06-fold odds (i.e., 16.67-fold lower odds) of having all RNFL thickness parameters considered normal by the machine. Furthermore, the odds of having at least one parameter considered as borderline or abnormal were 31-fold higher in subjects with than without glaucoma.

The Figure illustrates the relationship between pretest and posttest probabilities of disease when average RNFL thickness (Fig. A) or when at least one RNFL parameter (Fig. B) was considered borderline or abnormal by the machine (positive test) when it was considered normal by the machine (negative test). For instance, a pretest probability of the disease increased substantially from 30% to a posttest probability of 73.2% when average RNFL was considered abnormal and decreased from 30% to 8.9% when average RNFL was considered normal. More interestingly, whereas the probability of the disease increased from 30% to 58.1% when at least one RNFL parameter was considered abnormal or borderline, the probability of the disease strongly decreased from 70% to 12.3% when all RNFL parameters were considered normal.

Discussion

Our study shows good diagnostic performances of SD-OCT to discriminate glaucoma and control subjects in a general population of elderly subjects. We observed best AUC for average peripapillary, temporal-inferior, and temporal-superior RNFL thickness parameters, with values comparable with most previously published case-control studies. Quite a few case-control studies have already reported good discriminating performances of SD-OCT and have thus validated its usefulness in glaucoma diagnosis.[16–29] Despite differences in study methodology design, SD-OCT machines evaluated, population sample selected or severity of glaucoma disease in each glaucoma group, all these studies have validated high diagnostic performances of OCT imaging technology with best values of AUC ranging from 0.786 to 0.978. Furthermore, the average peripapillary RNFL thickness was the most frequently described discriminating parameter followed by temporal parameters. Results of our population-based study are in accordance with all these previously published studies and confirm the diagnostic performance of SD-OCT to discriminate between glaucoma and control subjects in a larger and representative population sample. Although case-control studies are necessary for an initial evaluation of a diagnostic test by providing very useful information on its accuracy, it has also been demonstrated that this methodology design is dependent on severity of cases recruited and of the representativeness of controls and thus might induce up to a 3-fold overestimation of the test power as compared with studies using a clinical cohort of population.[34] Furthermore, Michelessi et al.[33] reported in a systematic review of studies evaluating imaging technology for diagnosing glaucoma, that most of them had a high risk of bias mainly related to patient selection. Actually, spectrum bias, the most frequent cause of diagnostic accuracy overestimation, may be generated by an inappropriate selection of cases and controls and by a higher prevalence of the disease in a referral center where more severe cases are recruited.[44–47] Additionally, an unequal recruitment of case and control patients in the studied population may also improve the statistical power of the diagnostic test when there is more than one control patient per case patient selected. Our study was performed using an unselected population of elderly people randomly recruited from electoral rolls and individually contacted for enrollment in the study cohort with a longitudinal follow-up visit every 2 years.[39] Hence, the study design we used improved representativeness of our population sample of elderly people and allowed a more precise estimation of glaucoma prevalence in this age group. Thus, by limiting the risk of spectrum bias, we speculate our results may be more applicable in a real-life situation for glaucoma screening purposes in elderly populations. Some other population-based studies have reported diagnostic accuracy of OCT imaging technology.[30–32] By using a time-domain OCT, Li et al.[32] demonstrated moderate sensitivity but high specificity values of the machine to diagnose glaucoma in high-risk populations defined by either a family history of glaucoma or self-described from Caribbean and African origin; and Bengtsson et al.[31] found similar results in a younger cohort of glaucoma patients. More interestingly, Springelkamp et al.[30] observed high discriminating performances of SD-OCT by analyzing regional layer thicknesses of the peripapillary and macula area in a general population with AUC of 0.77 and 0.85, respectively. In our population sample, we observed higher AUC values of peripapillary RNFL thickness parameters, which was more likely related to a difference in the selection of the eye chosen for analysis of each participant. Hence, while Springelkamp et al.[30] analyzed a random eye of each participant, we selected the most affected eye of each participant defined by the lowest average RNFL thickness between the two eyes, if eligible, for analysis. Thus, we assume our methodology may be more appropriate for real-life screening purposes and may also have provided greater statistical power to the study. Indeed, a random selection

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TABLE 4. Cutoff Values at Best Sensitivity and Specificity, AUCs, Predictive Values, and LRs for Each RNFL Parameter to Discriminate Control and Glaucoma Eyes

RFNL Thickness µm Mean (SD)	AUC (95% CI)	Optimal RNFL Thickness Values, µm	Sensitivity, % (range)	Specificity, % (range)	Predictive Values, % (range)		Likelihood Ratios		DOR
					Positive	Negative	Positive	Negative	
Average	**0.895** (0.845; 0.945)	75	77.5 (62.5–87.7)	**87.8** (84.6–90.4)	**34.1** (24.0–45.0)	98.0 (96.2–99.1)	**6.36** (4.76–8.50)	0.26 (0.14–0.46)	24.80 (11.26–54.63)
Quadrant									
Temporal	0.742 (0.643; 0.840)	54	62.5 (47.0–75.8)	81.5 (77.8–84.7)	21.6 (14.5–30.2)	96.4 (94.1–98.0)	3.38 (2.50–4.58)	0.46 (0.31–0.69)	7.34 (3.72–14.49)
Nasal	0.756 (0.682; 0.829)	67	**92.5** (80.1–97.4)	44.9 (40.6–49.3)	12.0 (8.6–16.2)	98.7 (96.1–99.7)	1.68 (1.49–1.89)	0.17 (0.06–0.50)	10.06 (3.06–33.06)
Sectorial									
TS	0.868 (0.801; 0.935)	98	85.0 (70.9–92.9)	81.7 (78.1–84.9)	27.4 (19.8–36.2)	98.5 (96.8–99.5)	4.65 (3.70–5.84)	0.18 (0.09–0.38)	**25.31** (10.32–62.10)
TI	0.874 (0.808; 0.941)	103	85.0 (70.9–92.9)	80.5 (76.8–83.8)	26.2 (18.8–34.6)	98.5 (96.8–99.4)	4.36 (3.49–5.44)	0.19 (0.09–0.39)	23.38 (9.54–57.27)
NS	0.799 (0.738; 0.860)	85	87.5 (73.9–94.5)	60.8 (56.0–65.0)	15.4 (10.9–20.7)	98.4 (96.2–99.5)	2.23 (1.90–2.61)	0.21 (0.09–0.47)	10.85 (4.18–28.16)
NI	0.807 (0.745; 0.869)	91	**92.5** (80.1–97.4)	59.1 (54.8–63.4)	15.5 (11.2–20.8)	**99.0** (97.0–99.8)	2.26 (1.97–2.6)	**0.13** (0.04–0.38)	17.86 (5.43–58.71)

Results in bold show the best value for each measure of accuracy of RNFL parameters.

strategy of only one eye for each participant is more likely to miss glaucoma patient. As glaucoma is a frequent and irreversible cause of blindness or visual impairment, we also speculate this screening strategy could improve sensitivity of SD-OCT to detect glaucoma and could better prevent visual disability in a general population of elderly people with a higher prevalence of the disease than population of lower age.

Our study also provides an additional indicator of diagnostic performances by calculating likelihood ratios and DOR for each SD-OCT RNFL parameter. To our knowledge, this type of analysis has never been performed in a large unselected population of elderly people. Although sensitivity, specificity, and AUC provide strong information on diagnostic performances of a test, these values offer limited clinical application and may also overestimate the benefit of a test.[48] Unlike predictive values of a test, which are dependent on disease prevalence and provide test characteristics to the analyzed population only, likelihood ratios also allow a quantitative estimation for a patient to have the disease without the influence of its prevalence.[49] As glaucoma is characterized by an array of diagnosis uncertainty, the contribution of likelihood ratios of SD-OCT alone or combined with other diagnostic tests may improve the decision-making process to diagnose, treat, or follow patients more appropriately using posttest probability results.[50] Therefore, the pretest probability could be estimated either by the prevalence of the disease in a population or a subgroup of population or by the posttest probability of another test that could become the pretest probability of the current test. In our study, despite high AUC values, we observed a moderate influence of RNFL parameters on posttest probabilities when applying likelihood ratios. Hence, our findings demonstrate the clinical value of SD-OCT to discriminate between glaucoma and control subjects. Yet, in order to improve posttest probability of the disease, our study also illustrates a probably better clinical value of SD-OCT for screening glaucoma if it is combined with additional testing or performed in high-risk populations with an expected higher prevalence of the disease.

We also observed good diagnostic performances of the normative database provided by the machine for each RNFL parameter with a substantial influence on posttest probability of the disease in elderly people. Interestingly, regarding the average RNFL, the cutoff used by the normative database of the device (75 µm) corresponds to the optimal cutoff we identified using the Youden's index (Table 4), thus validating the performance of the normative database for this parameter. Finally, the combination of RNFL parameters of the normative database improved discriminating performances of the machine with DOR reaching 31.03 and 23.32, mainly related to low negative likelihood ratios at 0.06 and 0.14, if at least one parameter had a cutoff *P* value lower than 5% or 1%, respectively. This means that patients with all RNFL thickness parameters considered normal by the machine could be excluded from additional testing due to a very low LR− that strongly decreases the posttest probability of the disease. Although previous studies reported diagnostic accuracy of the normative database, none provided its validity in such a population-based sample of elderly subjects. In younger population samples, Moreno-Montanes et al.[26] reported a LR+ at 7.87, and Wu et al.[28] observed a sensitivity value at 80.3% and a specificity value at 92.9% for an average RNFL thickness parameter considered abnormal at the 5% level. Finally, the latter also demonstrated improved performances when combining RNFL parameter criteria. In their study, if at least one sector had an RNFL thickness considered abnormal, positive and negative likelihood ratios were 18.81 and 0.12, respectively[28].

Table 5. Ability of SD-OCT to Diagnose Glaucoma Using Statistically Abnormal Measurements

RFNL Thickness µm Mean (SD)	Cutoff *P* Value*	Corresponding RNFL Thickness Values, µm	Sensitivity, % (range)	Specificity, % (range)	Predictive Values, % (range)		Likelihood Ratios		DOR
					Positive	Negative	Positive	Negative	
Average	≤1%	75	77.5 (62.5–87.7)	87.8 (84.6–90.4)	34.1 (0.24–0.45)	98.0 (96.2–99.1)	6.36 (4.76–8.49)	0.26 (0.14–0.46)	**24.80** (11.26–54.63)
	≤5%	81	82.5 (67.2–92.6)	75.4 (71.3–79.2)	21.4 (15.2–28.8)	98.2 (96.2–99.2)	3.36 (2.72–4.14)	0.23 (0.12–0.46)	14.46 (6.23–33.52)
Quadrants									
Temporal	≤1%	44–45	27.5 (14.6–43.9)	**97.0** (95.0–98.3)	**42.3** (23.4–63.1)	94.3 (91.9–96.1)	**9.02** (4.44–18.31)	0.75 (0.62–0.91)	12.06 (5.09–28.61)
	≤5%	53	57.5 (40.9–73.0)	83.5 (80.0–86.7)	22.1 (14.6–31.3)	96.0 (93.7–97.7)	3.49 (2.50–4.87)	0.51 (0.35–0.73)	6.87 (3.51–13.42)
Nasal	≤1%	39–40	20.0 (9.0–35.6)	95.9 (93.8–97.5)	28.6 (13.2–48.7)	93.6 (91.2–95.6)	4.92 (2.32–10.46)	0.83 (0.71–0.98)	5.90 (2.41–14.44)
	≤5%	49–50	37.5 (22.7–54.2)	89.0 (85.9–91.6)	21.7 (12.7–33.3)	94.6 (92.1–96.5)	3.42 (2.13–5.48)	0.70 (0.55–0.89)	4.87 (2.42–9.80)
Sectorial									
TS	≤1%	95	77.5 (61.5–89.2)	86.4 (83.0–89.3)	31.6 (22.6–41.8)	97.9 (96.1–99.0)	5.69 (4.31–7.52)	0.26 (0.15–0.46)	21.85 (9.96–47.93)
	≤5%	103	**85.0** (70.2–94.3)	73.2 (69.0–77.0)	20.5 (14.6–27.4)	**98.4** (96.5–99.4)	3.17 (2.61–3.85)	0.21 (0.10–0.43)	15.46 (6.34–37.65)
TI	≤1%	101–102	77.5 (61.6–89.2)	82.5 (78.9–85.8)	26.5 (18.9–35.4)	97.8 (95.9–99.0)	4.43 (3.44–5.72)	0.27 (0.15–0.49)	16.26 (7.47–35.39)
	≤5%	106	**85.0** (70.2–94.3)	75.4 (71.4–79.2)	21.9 (15.7–29.3)	**98.4** (96.6–99.4)	3.46 (2.82–4.23)	**0.20** (0.10–0.42)	17.38 (7.12–41.39)
NS	≤ 1%	59	37.5 (22.7–54.2)	92.9 (90.2–95.0)	30.0 (17.9–44.6)	94.8 (92.4–96.6)	5.27 (3.16–8.80)	0.67 (0.53–0.86)	7.83 (3.79–16.20)
	≤5%	77	62.5 (45.8–77.3)	74.8 (70.7–78.6)	16.9 (11.2–23.8)	96.1 (93.6–97.8)	2.48 (1.87–3.30)	0.50 (0.34–0.75)	4.95 (2.53–9.68)
NI	≤1%	53	12.5 (4.2–26.8)	96.7 (94.8–98.1)	23.8 (8.2–47.2)	93.2 (90.6–95.2)	3.84 (1.49–9.95)	0.90 (0.80–1.02)	4.25 (1.47–12.28)
	≤5%	69	42.5 (27.0–59.1)	89.6 (86.6–92.2)	25.0 (15.3–37.0)	95.0 (92.6–96.8)	4.10 (2.63–6.39)	0.64 (0.49–0.84)	6.39 (3.20–12.75)
At least one RNFL parameter ≤5%			**97.5** (86.8–99.9)	44.3 (39.9–48.8)	12.5 (9.0–16.6)	**99.5** (97.5–99.9)	1.75 (1.60–1.92)	**0.06** (0.01–0.39)	**31.03** (4.23–227.65)
At least one RNFL parameter ≤1%			90.0 (76.3–97.2)	**72.2** (68.0–76.1)	**20.8** (15.0–27.6)	98.9 (97.2–99.7)	**3.23** (2.71–3.85)	0.14 (0.06–0.35)	23.32 (8.15–66.75)

Measurements provided by RNFL analysis printout of OCT device (Heidelberg Engineering). Results in bold show the best value for each measure of accuracy of RNFL parameters and the combination of RNFL parameters.

* Considered abnormal (≤1%) or borderline (≤5%) by the machine.

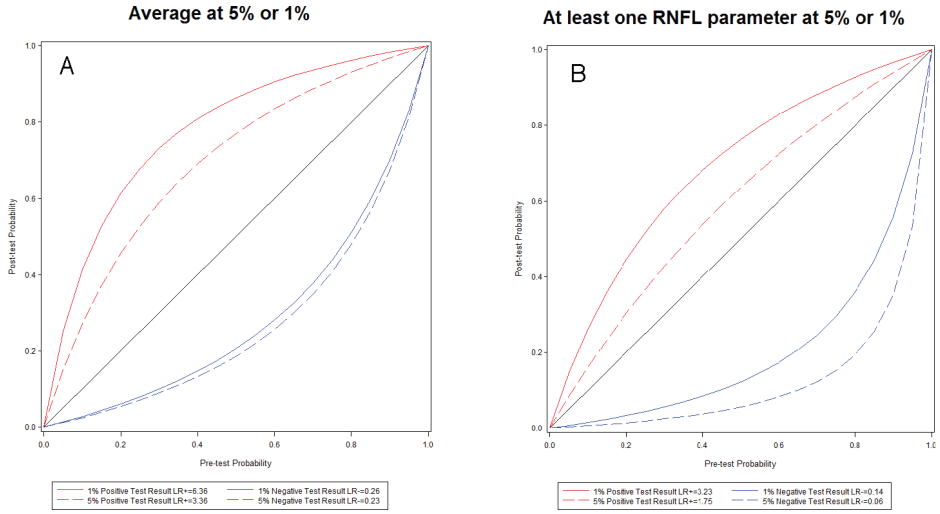

Figure. Relationship between pretest probability of the disease and posttest probability of the disease when the average RNFL parameter was considered borderline (5% cutoff *P* value) or outside normal limit (1% cutoff *P* value) by the machine (**A**) and when at least one RNFL parameter was considered borderline (5% cutoff *P* value) or abnormal (1% cutoff *P* value) by the machine (**B**). The likelihood ratios for positive (*red line*) and negative (*blue line*) test results are shown.

Although we analyzed diagnostic performances of SD-OCT to detect glaucoma in a general and unselected elderly population, our study may have some limitations that need to be considered. First, the influence of corneal curvature, longer axial length, high myopia, or peripapillary atrophy on peripapillary RNFL thickness measurements can bias diagnostic performances of SD-OCT to detect glaucoma.[51–53] Although a small percentage of the general population may be concerned, the applicability of our findings in a screening strategy has to take into account these factors that could affect accuracy of SD-OCT measurements. However, Nowroozizadeh et al.[54] showed that in a specialized glaucoma center—where cases are usually more severe and less representative of a general population—the correction of ocular magnification effect did not improve prediction limits in normal subjects or enhance performances of SD-OCT RNFL measurements. Hence, in the range of commonly found variation in axial length or corneal curvature observed in a general population, we thus hypothesize that our measurements are less influenced by the ocular magnification effect and therefore that this screening strategy can be applied in a general population even in elderly who frequently have a history of cataract surgery. Additionally, due to a high prevalence of macular abnormalities in our cohort of elderly people, we could not analyze performances of macular parameters, such as ganglion cell complex layer thickness, or combine them with RNFL parameters to improve glaucoma detection. All stages of AMD are frequent in elderly subjects and prevalence of early and late AMD can reach 29.7% and 7.1%, respectively for people older than 75 years and 37.1% to 30.8% for people older than 80 years.[35–38] Consequently, these abnormalities may partly affect SD-OCT measurements of retinal ganglion cell thickness and can make this parameter not clinically applicable in a real-life situation or not useful in a screening strategy for glaucoma in such populations. However, RNFL parameters are more frequently described as having the best diagnostic accuracy and our results showed good diagnostic performances of these parameters.[18,19,21,27] Finally, in our study design, we used the International Society for Epidemiologic and Geographical Ophthalmology classification to define glaucoma and most of our glaucoma cases were classified in category 1 associating structural and functional evidence to confirm the disease.[41] Two other cases were classified in category 2 or 3, with advanced structural damage or unproven visual field loss. As diagnostic tests tend to be more sensitive in more advanced stages of the disease, the measures of diagnostic performances of SD-OCT in our study, which mainly includes perimetric glaucoma cases, may be less applicable to preperimetric glaucoma cases.

In conclusion, SD-OCT RNFL parameters had good diagnostic performances to discriminate glaucoma and control subjects in a general and unselected population of elderly people. By providing a posttest probability, SD-OCT may be a valuable tool in a screening program to improve the detection of glaucoma in such populations, particularly when all RNFL parameters are combined. Further evaluations are warranted to help clinicians and decision makers define the most appropriate and cost-effective screening strategy in high-risk populations to prevent glaucoma-related visual disabilities and their socioeconomic consequences.

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References

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology.* 2014;121:2081–2090.

2. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90:262–267.
3. Leske MC, Wu SY, Hennis A, Honkanen R, Nemesure B; BESs Study Group. Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. *Ophthalmology*. 2008;115:85–93.
4. de Voogd S, Ikram MK, Wolfs RC, Jansonius NM, Hofman A, de Jong PT. Incidence of open-angle glaucoma in a general elderly population: the Rotterdam Study. *Ophthalmology*. 2005;112:1487–1493.
5. Doshi V, Ying-Lai M, Azen SP, Varma R; Los Angeles Latino Eye Study Group. Sociodemographic, family history and lifestyle risk factors for open-angle glaucoma and ocular hypertension. The Los Angeles Latino Eye Study. *Ophthalmology*. 2008;115:639–647.e2.
6. Weih LM, Nanjan M, McCarty CA, Taylor HR. Prevalence and predictors of open-angle glaucoma: results from the visual impairment project. *Ophthalmology*. 2001;108:1966–1972.
7. Jacobs JM, Hammerman-Rozenberg R, Maaravi Y, Cohen A, Stessman J. The impact of visual impairment on health function and mortality. *Aging Clin Exp Res*. 2005;17:281–286.
8. Rubin GS, Bandeen-Roche K, Huang GH, et al. The association of multiple visual impairments with self-reported visual disability: SEE project. *Invest Ophthalmol Vis Sci*. 2001;42:64–72.
9. Ivers RQ, Cumming RG, Mitchell P, Attebo K. Visual impairment and falls in older adults: the Blue Mountains Eye Study. *J Am Geriatr Soc*. 1998;46:58–64.
10. Klein BE, Moss SE, Klein R, Lee KE, Cruickshanks KJ. Associations of visual function with physical outcomes and limitations 5 years later in an older population: the Beaver Dam eye study. *Ophthalmology*. 2003;110:644–650.
11. Reus NJ, Lemij HG, Garway-Heath DF, et al. Clinical assessment of stereoscopic optic disc photographs for glaucoma: the European Optic Disc Assessment Trial. *Ophthalmology*. 2010;117:717–723.
12. Azuara-Blanco A, Katz LJ, Spaeth GL, Vernon SA, Spencer F, Lanzl IM. Clinical agreement among glaucoma experts in the detection of glaucomatous changes of the optic disk using simultaneous stereoscopic photographs. *Am J Ophthalmol*. 2003;136:949–950.
13. Zeyen T, Miglior S, Pfeiffer N, Cunha-Vaz J, Adamsons I; European Glaucoma Prevention Study Group. Reproducibility of evaluation of optic disc change for glaucoma with stereo optic disc photographs. *Ophthalmology*. 2003;110:340–344.
14. Gabriele ML, Wollstein G, Ishikawa H, et al. Three dimensional optical coherence tomography imaging: advantages and advances. *Prog Retin Eye Res*. 2010;29:556–579.
15. van Velthoven ME, Faber DJ, Verbraak FD, van Leeuwen TG, de Smet MD. Recent developments in optical coherence tomography for imaging the retina. *Prog Retin Eye Res*. 2007;26:57–77.
16. Simavli H, Que CJ, Akduman M, et al. Diagnostic capability of peripapillary retinal thickness in glaucoma using 3D volume scans. *Am J Ophthalmol*. 2015;159:545–556.e2.
17. Rao HL, Yadav RK, Addepalli UK, et al. Peripapillary retinal nerve fiber layer assessment of spectral domain optical coherence tomography and scanning laser polarimetry to diagnose preperimetric glaucoma. *PLoS One*. 2014;9:e108992.
18. Nouri-Mahdavi K, Nowroozizadeh S, Nassiri N, et al. Macular ganglion cell/inner plexiform layer measurements by spectral domain optical coherence tomography for detection of early glaucoma and comparison to retinal nerve fiber layer measurements. *Am J Ophthalmol*. 2013;156:1297–1307.e2.
19. Akashi A, Kanamori A, Nakamura M, Fujihara M, Yamada Y, Negi A. Comparative assessment for the ability of Cirrus, RTVue and 3D-OCT to diagnose glaucoma. *Invest Ophthalmol Vis Sci*. 2013;54:4478–4484.
20. Jeoung JW, Choi YJ, Park KH, Kim DM. Macular ganglion cell imaging study: glaucoma diagnostic accuracy of spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2013;54:4422–4429.
21. Lisboa R, Paranhos A Jr, Weinreb RN, Zangwill LM, Leite MT, Medeiros FA. Comparison of different spectral domain OCT scanning protocols for diagnosing preperimetric glaucoma. *Invest Ophthalmol Vis Sci*. 2013;54:3417–3425.
22. Leite MT, Rao HL, Zangwill LM, Weinreb RN, Medeiros FA. Comparison of the diagnostic accuracies of the Spectralis, Cirrus, and RTVue optical coherence tomography devices in glaucoma. *Ophthalmology*. 2011;118:1334–1349.
23. Mwanza JC, Oakley JD, Budenz DL, Anderson DR; Cirrus Optical Coherence Tomography Normative Database Study Group. Ability of cirrus HD-OCT optic nerve head parameters to discriminate normal from glaucomatous eyes. *Ophthalmology*. 2011;118:241–248.e1.
24. Leung CK, Ye C, Weinreb RN, et al. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography a study on diagnostic agreement with Heidelberg Retinal Tomograph. *Ophthalmology*. 2010;117:267–274.
25. Leung CK, Cheung CY, Weinreb RN, et al. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: a variability and diagnostic performance study. *Ophthalmology*. 2009;116:1257–1263.
26. Moreno-Montanes J, Olmo N, Alvarez A, Garcia N, Zarranz-Ventura J. Cirrus high-definition optical coherence tomography compared with Stratus optical coherence tomography in glaucoma diagnosis. *Invest Ophthalmol Vis Sci*. 2010;51:335–343.
27. Rao HL, Zangwill LM, Weinreb RN, Sample PA, Alencar LM, Medeiros FA. Comparison of different spectral domain optical coherence tomography scanning areas for glaucoma diagnosis. *Ophthalmology*. 2010;117:1692–1699.
28. Wu H, de Boer JF, Chen TC. Diagnostic capability of spectral-domain optical coherence tomography for glaucoma. *Am J Ophthalmol*. 2012;153:815–826.e2.
29. Mwanza JC, Durbin MK, Budenz DL, et al. Glaucoma diagnostic accuracy of ganglion cell-inner plexiform layer thickness: comparison with nerve fiber layer and optic nerve head. *Ophthalmology*. 2012;119:1151–1158.
30. Springelkamp H, Lee K, Wolfs RC, et al. Population-based evaluation of retinal nerve fiber layer, retinal ganglion cell layer, and inner plexiform layer as a diagnostic tool for glaucoma. *Invest Ophthalmol Vis Sci*. 2014;55:8428–8438.
31. Bengtsson B, Andersson S, Heijl A. Performance of time-domain and spectral-domain optical coherence tomography for glaucoma screening. *Acta Ophthalmol*. 2012;90:310–315.
32. Li G, Fansi AK, Boivin JF, Joseph L, Harasymowycz P. Screening for glaucoma in high-risk populations using optical coherence tomography. *Ophthalmology*. 2010;117:453–461.
33. Michelessi M, Lucenteforte E, Oddone F, et al. Optic nerve head and fibre layer imaging for diagnosing glaucoma. *Cochrane Database Syst Rev*. 2015;11:CD008803.
34. Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA*. 1999;282:1061–1066.
35. Jonasson F, Arnarsson A, Sasaki H, Peto T, Sasaki K, Bird AC. The prevalence of age-related maculopathy in iceland: Reykjavik eye study. *Arch Ophthalmol*. 2003;121:379–385.
36. Merle B, Delyfer MN, Korobelnik JF, et al. Dietary omega-3 fatty acids and the risk for age-related maculopathy: the Alienor Study. *Invest Ophthalmol Vis Sci*. 2011;52:6004–6011.
37. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. *Ophthalmology*. 1995;102:1450–1460.

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38. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology*. 1992;99:933–943.
39. Delcourt C, Korobelnik JF, Barberger-Gateau P, et al. Nutrition and age-related eye diseases: the ALIENOR (Antioxydants, Lipides Essentiels, Nutrition et maladies Oculaires) Study. *J Nutr Health Aging*. 2010;14:854–861.
40. 3C Study Group. Vascular factors and risk of dementia: design of the Three-City study and baseline characteristics of the study population. *Neuroepidemiology*. 2003;22:316–325.
41. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol*. 2002;86:238–242.
42. Simel DL, Samsa GP, Matchar DB. Likelihood ratios with confidence: sample size estimation for diagnostic test studies. *J Clin Epidemiol*. 1991;44:763–770.
43. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol*. 2003;56:1129–1135.
44. Medeiros FA, Ng D, Zangwill LM, Sample PA, Bowd C, Weinreb RN. The effects of study design and spectrum bias on the evaluation of diagnostic accuracy of confocal scanning laser ophthalmoscopy in glaucoma. *Invest Ophthalmol Vis Sci*. 2007;48:214–222.
45. Leite MT, Zangwill LM, Weinreb RN, et al. Effect of disease severity on the performance of Cirrus spectral-domain OCT for glaucoma diagnosis. *Invest Ophthalmol Vis Sci*. 2010;51:4104–4109.
46. Rao HL, Kumbar T, Addepalli UK, et al. Effect of spectrum bias on the diagnostic accuracy of spectral-domain optical coherence tomography in glaucoma. *Invest Ophthalmol Vis Sci*. 2012;53:1058–1065.
47. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med*. 1978;299:926–930.
48. Khan KS, Khan SF, Nwosu CR, Arnott N, Chien PF. Misleading authors' inferences in obstetric diagnostic test literature. *Am J Obstet Gynecol*. 1999;181:112–115.
49. Grimes DA, Schulz KF. Refining clinical diagnosis with likelihood ratios. *Lancet*. 2005;365:1500–1505.
50. Lisboa R, Mansouri K, Zangwill LM, Weinreb RN, Medeiros FA. Likelihood ratios for glaucoma diagnosis using spectral-domain optical coherence tomography. *Am J Ophthalmol*. 2013;156:918–926.e2.
51. Lai E, Wollstein G, Price LL, et al. Optical coherence tomography disc assessment in optic nerves with peripapillary atrophy. *Ophthalmic Surg Lasers Imaging*. 2003;34:498–504.
52. Leung CK, Mohamed S, Leung KS, et al. Retinal nerve fiber layer measurements in myopia: An optical coherence tomography study. *Invest Ophthalmol Vis Sci*. 2006;47:5171–5176.
53. Patel NB, Garcia B, Harwerth RS. Influence of anterior segment power on the scan path and RNFL thickness using SD-OCT. *Invest Ophthalmol Vis Sci*. 2012;53:5788–5798.
54. Nowroozizadeh S, Cirineo N, Amini N, et al. Influence of correction of ocular magnification on spectral-domain OCT retinal nerve fiber layer measurement variability and performance. *Invest Ophthalmol Vis Sci*. 2014;55:3439–3446.

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