

# Frequency-Doubling Threshold Perimetry in Predicting Glaucoma in a Population-Based Study

## *The Beijing Eye Study*

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**Objective:** To determine the predictive value of frequency-doubling threshold perimetry for glaucoma in a population-based study.

**Methods:** The Beijing Eye Study, a population-based study on subjects 40 years or older, included an ophthalmic examination with fundus photography and frequency-doubling threshold perimetry. Glaucoma was defined by a glaucomatous optic disc appearance.

**Results:** The study population consisted of 4349 subjects (8615 eyes). Among 207 glaucomatous eyes (2.4%), 74 (35.7%) did not show any abnormality on frequency-doubling threshold perimetry, suggesting a diagnostic sensitivity of 64.3%. In the total study population, a visual field defect was found in 905 eyes (10.5%). In 133 (14.7%) of these eyes, a glaucomatous appearance of the optic

disc was detected, and 772 eyes (85.3%) had a nonglaucomatous optic disc appearance (either normal or with nonglaucomatous optic nerve damage, retinal disease, corneal disease, or cataract). For 450 eyes (49.7%) with a visual field defect, the cause of the perimetric defect was not detected.

**Conclusions:** In a population-based study, frequency-doubling threshold perimetry has a sensitivity of about 64% to detect glaucoma. If the result is abnormal, the probability of glaucoma is about 15%. When results of frequency-doubling threshold perimetry are abnormal, the cause of the visual field defect may not be detectable in 50% of subjects.

*Arch Ophthalmol.* 2007;125(10):1402-1406

**T**HE DIAGNOSIS OF GLAUCOMA has been based on the assessment of glaucomatous abnormalities or changes in morphologic characteristics of the optic nerve head, measurement of intraocular pressure, and detection of visual field defects. For detection of glaucomatous visual field loss, frequency-doubling threshold perimetry has been introduced into clinical ophthalmology,<sup>1-4</sup> and its diagnostic value has been convincingly demonstrated in hospital-based investigations.<sup>5-12</sup> The advantage of hospital-based studies in including a relatively large number of patients is, however, countered by the disadvantage of a possible selection bias caused by the referral pattern of the ophthalmologists, so that the characteristics of the subjects included in hospital studies are not representative of those of the population at large. The results may therefore not be representative of the real-world situation. The purpose of the present study was to assess the diagnostic utility of frequency-doubling threshold perimetry for

the detection of glaucoma in a population-based investigation.

## METHODS

The Beijing Eye Study is a population-based cross-sectional study in northern China. The study has been described in detail recently.<sup>13-17</sup> The Medical Ethics Committee of the Beijing Tongren Hospital approved the study protocol, and all participants gave informed consent according to the Declaration of Helsinki. A total population of 5324 individuals 40 years or older was asked to participate, of which 4439 individuals (2505 of them women) took part in the investigation (response rate, 83.4%). The study was divided into a rural part (1973 subjects) and an urban part (2466 subjects). Mean age was 56 ± 11 years (median, 56 years; range, 40-101 years).

The study design and the methods applied have been described in detail recently.<sup>13-19</sup> Visual field examinations were performed by frequency-doubling threshold perimetry using the screening program C-20-1 (Zeiss-Humphrey, Dublin, California). The rate of false-positive results had to be 0.33 or less, and the rate of fixa-

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tion loss had to be 0.33 or lower. A participant with any abnormal or unreliable result on frequency-doubling threshold perimetry repeated the test, and the results of the second test were taken for further statistical analysis. We defined an abnormal frequency-doubling threshold perimetry result as at least 1 test location of reduced sensitivity; in a second step, we defined an abnormal result as at least 2 abnormal test locations. The Snellen method was used for measurement of visual acuity. Optic disc slides were qualitatively examined as described in detail previously.<sup>20,21</sup> The optic disc assessment was performed by a single examiner (Y.W.) after a training period with 2 glaucoma specialists (L.X. and J.B.J.). In a second step of the examination, in case of doubt, the optic disc photographs were reassessed by a panel (including L.X. and J.B.J.). In a third step of the examination, the optic disc photographs of all eyes with suspicious optic nerve heads, of all highly myopic eyes, of all eyes with an intraocular pressure higher than 21 mm Hg, and of all eyes with visual field loss or a visual acuity of less than 0.50 (20/40 or 3/6) were separately rereviewed (by L.X., J.B.J., and coworkers).

Glaucoma was defined morphologically, ie, the only criterion for glaucoma was a glaucomatous appearance of the optic disc. Absolute criteria for a glaucomatous appearance of the optic nerve head, each of which was sufficient for the diagnosis of glaucoma, were a notch in the neuroretinal rim in the temporal inferior region and/or the temporal superior region, so that the ISNT rule (inferior-superior-nasal-temporal rule) was not fulfilled (in eyes with an optic cup sufficiently large to allow an assessment of the neuroretinal shape); a localized retinal nerve fiber layer defect that could not be explained by any other cause than glaucoma; and an abnormally large cup in relation to the size of the optic disc.<sup>15,20,21</sup> Relative criteria for the diagnosis of a glaucomatous appearance of the optic nerve head were a neuroretinal rim that was markedly thinner in the inferior disc region than in the superior disc region, even if the smallest part of the neuroretinal rim was located in the temporal horizontal disc region (suspicious neuroretinal rim shape); a diffuse decrease in the visibility of the retinal nerve fiber layer (particularly in eyes with small optic discs), if the background pigmentation of the eye allowed an assessment of the retinal nerve fiber layer and if there were no reasons other than glaucoma for retinal nerve fiber layer loss; a marked diffuse thinning and/or focal thinning of the retinal arteries, if there were no reasons other than glaucoma for retinal vessel thinning; an optic disc hemorrhage, if there were no other reasons for disc bleeding, such as retinal vessel occlusions; and occurrence of an optic cup in a small optic disc that usually would not show cupping. If none of the absolute glaucoma criteria was present, at least 2 relative criteria had to be present, including a suspicious neuroretinal rim shape in eyes with an optic cup large enough for the assessment of the rim shape; or at least 2 relative criteria had to be present, including the occurrence of an optic cup in a small optic disc that usually would not show cupping. The intraocular pressure and presence of visual field defects were not used as criteria for the diagnosis of glaucoma.

Inclusion criteria for the present study were available visual field examinations with a false-positive rate of 0.33 or less, a rate of fixation loss of 0.33 or less, and assessable optic disc photographs. Results are given as mean  $\pm$  SE unless otherwise indicated.

## RESULTS

Data on the visual field were available for 8719 eyes of 4368 subjects (98.4% of the total of 4439 subjects). For further analysis, 104 eyes with a false-positive rate higher than 0.33 and a rate of fixation loss higher than 0.33 were excluded, so that the study population with assessable

**Table. Cross Table of Frequency-Doubling Threshold Perimetry With Glaucomatous Optic Neuropathy in the Beijing Eye Study**

Result of Perimetry	Diagnosis		Total
	Glaucomatous	Nonglaucomatous	
<b>Results by Number of Eyes<sup>a</sup></b>			
Abnormal	133	772	<b>905</b>
Normal	74	7636	<b>7710</b>
<b>Total</b>	<b>207</b>	<b>8408</b>	<b>8615</b>
<b>Results by Number of Subjects<sup>b</sup></b>			
Abnormal	95	586	<b>681</b>
Normal	37	3631	<b>3668</b>
<b>Total</b>	<b>132</b>	<b>4217</b>	<b>4349</b>

<sup>a</sup>Sensitivity, 64.3%; specificity, 90.8%; positive predictive value, 14.7%; negative predictive value, 99.0%.

<sup>b</sup>Sensitivity, 72.0%; specificity, 86.1%; positive predictive value, 14.0%; negative predictive value, 99.0%.

visual examination consisted of 8615 eyes of 4349 subjects (98.0% of the original study population). Of the 4349 subjects, 2434 were women; the mean age was  $56 \pm 10$  years (median age, 56.0 years; range, 40-89 years), and the mean refractive error was  $-0.37 \pm 2.30$  diopters (D) (median, 0.00 D; range,  $-20.13$  to  $+13.50$  D).

### STEP 1: ANALYSIS WITH 1 ABNORMAL TEST POINT

According to the definition of glaucoma used in this study, 207 (2.4%) of the eyes were glaucomatous. The prevalence rate was  $2.4\% \pm 0.2\%$  (95% confidence interval [CI], 2.1%-2.7%). Of the 207 glaucomatous eyes, 74 (35.7%) did not show any abnormality on frequency-doubling threshold perimetry, indicating a sensitivity of 64.3% to detect glaucoma (**Table**). These 74 eyes had significantly ( $P < .001$ ) less glaucomatous damage than did the glaucomatous eyes with visual field defects as measured by neuroretinal rim area and vertical cup to disc diameter ratio. Presence of glaucomatous optic nerve damage and presence of any visual field defect on frequency-doubling threshold perimetry were significantly associated with each other ( $P < .001$ ; odds ratio, 17.8; 95% CI, 13.3-23.9).

According to the same definition of glaucoma, 132 subjects had glaucoma, with a prevalence rate of  $3.0\% \pm 0.3\%$  (95% CI, 2.5%-3.5%). Of these 132 subjects, 37 (28.0%) did not show any abnormality on frequency-doubling threshold perimetry, indicating a sensitivity of 72.0% to detect glaucoma by subject (**Table**). These 37 subjects had significantly ( $P < .001$ ) less glaucomatous damage than did those with visual field defects, as measured by neuroretinal rim area and vertical cup to disc diameter ratio. Presence of glaucomatous optic nerve damage and presence of any visual field defect on frequency-doubling threshold perimetry were significantly associated with each other ( $P < .001$ ; odds ratio, 15.9; 95% CI, 10.8-23.5).

In the total study population, there were 905 eyes (10.5%) with a visual field abnormality (prevalence rate,  $10.5\% \pm 0.3\%$ ; 95% CI, 9.9%-11.2%). Of these 905 eyes, 133 (14.7%) showed a glaucomatous appearance of the optic disc and 772 (85.3%) had an optic disc that was

graded as nonglaucomatous (either normal or exhibiting signs of nonglaucomatous optic nerve damage). The prevalence rate for these eyes with abnormal results of frequency-doubling threshold perimetry and a nonglaucomatous appearance of the optic disc in the total study population was  $9.0\% \pm 0.3\%$  (95% CI, 8.4%-9.6%). Reasons for visual field defects in the eyes with a nonglaucomatous appearance of the optic disc were cataract, degenerative myopia, diabetic retinopathy, corneal opacities, retinal vein occlusions, age-related macular degeneration, epiretinal membranes, and nonglaucomatous optic nerve damage, such as presumed previous nonarteritic anterior ischemic optic neuropathy and optic disc drusen.<sup>16</sup>

For 450 of 905 eyes with a visual field defect (49.7%), the cause of the defect found by frequency-doubling threshold perimetry could not be detected. When these eyes were compared with the eyes with abnormal results of perimetric examination and a detected cause of the visual field loss, mean best-corrected visual acuity was significantly higher ( $0.89 \pm 0.19$  vs  $0.45 \pm 0.34$  Snellen line;  $P < .001$ ), mean refractive error showed significantly less myopia ( $-0.47 \pm 2.39$  vs  $-3.46 \pm 5.94$  D;  $P < .001$ ), mean refractive astigmatism was significantly lower ( $+0.81 \pm 0.86$  vs  $1.62 \pm 1.39$  D;  $P < .001$ ), and visual field loss score was significantly lower ( $P < .001$ ) in the subjects with no detected reason for an abnormal test result. The groups did not vary significantly in sex ( $P = .79$ ) and rural area vs urban area ( $P = .09$ ).

When statistical analysis was performed with the number of subjects used as the statistical unit, there were 681 subjects (15.7%) with a visual field abnormality (prevalence rate,  $15.7\% \pm 0.6\%$ ; 95% CI, 14.5%-16.9%) in the total study population. Of these 681 subjects, 95 (14.0%) showed a glaucomatous appearance of the optic disc. In 586 subjects (86.0%) with abnormal results of frequency-doubling threshold perimetry, the optic disc was graded as nonglaucomatous (either normal [ $n = 562$  (82.5%)] or exhibiting signs of nonglaucomatous optic nerve damage). The prevalence rate for these subjects with abnormal results of frequency-doubling threshold perimetry and a nonglaucomatous appearance of the optic disc in the total study population was  $13.5\% \pm 0.5\%$  (95% CI, 12.5%-14.5%). For 329 subjects (48.3%) with a visual field defect, the cause of the defect could not be detected. When these subjects were compared with the subjects who had a detected cause, mean best-corrected visual acuity was significantly higher ( $0.90 \pm 0.19$  vs  $0.56 \pm 0.34$  Snellen line;  $P < .001$ ), mean refractive error was significantly less myopic ( $-0.40 \pm 2.37$  vs  $-2.65 \pm 5.54$  D;  $P < .001$ ), mean refractive astigmatism was significantly lower ( $0.78 \pm 0.88$  vs  $1.41 \pm 1.27$  D;  $P < .001$ ), and visual field loss score was significantly lower ( $P < .001$ ) for the subjects with no detected reason for the abnormal test result. The groups did not vary significantly in sex ( $P = .19$ ) and rural area vs urban area ( $P = .11$ ).

## STEP 2: ANALYSIS WITH 2 ABNORMAL TEST POINTS

When an abnormal result of frequency-doubling threshold perimetry was defined as at least 2 abnormal test points, 103 among the 207 glaucomatous eyes (49.8%) did not

show an abnormal perimetry result, suggesting a diagnostic sensitivity of 50.2%. Using this more specific definition of an abnormal perimetric test result, a visual field defect was found in 555 eyes (6.4%) in the total study population. In 104 (18.7%) of these eyes, a glaucomatous appearance of the optic disc was detected, whereas 451 eyes (81.3%) had a nonglaucomatous optic disc appearance (either normal or with nonglaucomatous optic nerve damage, retinal disease, corneal disease, or cataract). For 146 eyes (26.3%) with a visual field defect, a cause of the perimetric defect was not detected.

Taking individuals as the unit of statistical analysis showed that, among the 132 subjects with glaucoma, 55 (41.7%) did not show an abnormal result of frequency-doubling threshold perimetry examination, suggesting a diagnostic sensitivity of 58.3% per subject. Using this more specific definition of an abnormal perimetric test result, a visual field defect was found in 420 subjects (9.7%) of the total study population. In 77 (18.3%) of these subjects, a glaucomatous appearance of the optic disc was detected and 343 subjects (81.7%) had a nonglaucomatous optic disc appearance (either normal or with nonglaucomatous optic nerve damage, retinal disease, corneal disease, or cataract). For 106 subjects (25.2%) with a visual field defect, the cause of the perimetric defect was not detected.

## WHITE-ON-WHITE STATIC PERIMETRY

One-hundred fifteen eyes of 79 subjects with an abnormal result of frequency-doubling threshold perimetry examination (defined as  $\geq 1$  abnormal test point) underwent white-on-white static computerized perimetry (Octopus program TOP G1; Interzeag Co, Schlieren, Switzerland). In 111 (96.5%) of the eyes and in 76 (96.2%) of the subjects, white-on-white perimetry confirmed the presence of a visual field abnormality. For 4 eyes (3.5%) or 4 subjects (5.1%) with an abnormal result of perimetry examination, results of white-on-white conventional perimetry were unremarkable.

## COMMENT

The data in the present study suggest that, in a population-based setting, frequency-doubling threshold perimetry may have a diagnostic sensitivity of 64.3% to detect glaucoma as defined by a glaucomatous appearance of the optic nerve head. It agrees with previous studies in several aspects.<sup>1-12,22-30</sup> Traditionally, glaucoma has been defined by optic disc changes and visual field defects. Histologic studies have shown, however, that there may be a significant loss of ganglion cells before evidence of functional loss is seen on conventional visual field testing.<sup>31,32</sup> For this reason attention has been focused on alternative, more sensitive ways of detecting early ganglion cell damage. In several studies on eyes with elevated intraocular pressure and normal visual fields, abnormal results in various psychophysical and electrophysiologic examinations were reported, such as in the pattern electroretinogram, in tests for color vision and flicker sensitivity, or in the swinging flashlight test.<sup>33-36</sup> As with the

newer psychophysical and electrophysiologic techniques, changes in optic disc variables, in particular the neuroretinal rim shape, optic disc hemorrhages, and defects in the retinal nerve fiber layer, have been described to precede visual field defects.<sup>37-42</sup>

The present population-based study in adult Chinese subjects in Greater Beijing confirms the previous findings, that the psychophysical technique of frequency-doubling threshold perimetry may not be able to detect all patients with a glaucomatous appearance of the optic nerve head. In that context, one must take into account that frequency-doubling threshold perimetry was designed to detect visual field status related to any ocular or neurologic disease and that its primary purpose was not to detect glaucoma.

Previous studies evaluating the value of frequency-doubling threshold perimetry for detecting glaucoma demonstrated high sensitivities and specificities of the method for the detection of early, moderate, and advanced glaucoma as defined by the presence of conventional visual field defects.<sup>23,24,29</sup> The differences between these previous studies and the present investigation, which found a relatively low sensitivity, may be in the composition of the study populations and the study design. Although the previous hospital-based studies conducted in glaucoma referral centers used frequency-doubling threshold perimetry to differentiate glaucomatous eyes from normal control eyes, the Beijing Eye Study was performed in communities, where participants were not selected. This explains why other eye diseases besides glaucoma were additional causes of visual field defects in the Beijing Eye Study. Correspondingly, diabetes mellitus without retinopathy and arterial hypertension have been reported to be associated with frequency-doubling threshold perimetry abnormalities.<sup>43</sup> Interestingly, results similar to those in the Beijing Eye Study were recently reported for the population-based Tajimi Study, in which the sensitivity and specificity values for detecting glaucoma were 55.6% and 92.7%, respectively.<sup>30</sup>

There are limitations of the present study. As in any population-based study, selection bias could have accentuated some estimates and masked others. The overall participation rate in our survey was 83.4%, and it is possible that nonparticipants had different rates and causes of visual field loss. However, the response was higher in the present study than in some other population-based investigations.<sup>29,44-61</sup> Another possible limitation is the definition of glaucoma, which was based on the qualitative assessment of the optic nerve head appearance in the present investigation in contrast to previous population-based studies on the prevalence of glaucoma.<sup>29,44-61</sup> However, the prevalence of glaucoma was not markedly different between the Beijing Eye Study and the other studies, so differences in the definition of glaucoma may not have markedly influenced the results of the study. Another possible limitation is the definition of a visual field defect in the present study, which was any abnormality in results of frequency-doubling threshold perimetry. With a more strict definition of a visual field defect, the sensitivity of the technique would have been lower to detect glaucoma, and, as a corollary, the number of normal eyes with abnormal visual field results would also have been lower. Finally, a

bias may have been introduced into the study because structure was used to define glaucoma. Structure and function loss in glaucoma are not always highly correlated: some patients will have visual field loss and no observable optic disc abnormalities and vice versa. This may hold true particularly for patients with small optic discs. The disadvantages of small optic discs in the detection of structural optic nerve head abnormalities in glaucoma have, however, specifically been addressed in the morphologic diagnosis of glaucoma.<sup>20</sup>

In conclusion, in the setting of a population-based study, frequency-doubling threshold perimetry may have a sensitivity of about 64% to detect glaucoma. If results of frequency-doubling threshold perimetry are abnormal, the probability of glaucoma may be about 15%. For 85% of the subjects with abnormal results of frequency-doubling threshold perimetry, other reasons for visual field defects were present, such as diabetic retinopathy, retinal vein occlusions, age-related macular degeneration, and cataract, or a cause of the visual field defect could not be found (which was the case in about 50% of the subjects).

**Submitted for Publication:** August 24, 2006; final revision received November 22, 2006; accepted December 17, 2006.

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**Financial Disclosure:** None reported.

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