imaging and in 2 subjects (2/60, 3.3%) by elevated IOPs. When the subjects with not available HRT II scans and not available nonsimultaneous stereoscopic photographs were excluded, glaucoma was detected in 46 subjects (46/48, 95.8%) by nonmydriatic stereoscopic photography and in 52 subjects (52/60, 86.7%) by HRT II imaging. When the subjects with poor quality nonsimultaneous stereoscopic photographs and unacceptable HRT II scans were excluded, glaucoma was detected in 46 subjects (46/48, 95.8%) by nonmydriatic stereoscopic photography and in 43 subjects (43/47, 91.5%) by HRT II imaging.

The sensitivity, specificity, PPV and NPV of HRT II are shown in Table 4. The sensitivity of nonmydriatic stereoscopic photography for personal-level analysis was 95.8% and that for eye-level analysis was 95.5%. Though the sensitivity for eye-level analysis of nonmydriatic stereoscopic fundus photography was significantly higher than that of HRT II (both MRA 1 and MRA 2, $P<0.001$), the sensitivity for personal-level analysis was not significantly higher than that of HRT II when "borderline" outcomes were treated as test positive ($P=0.654$).

## Discussion

The fact that most glaucoma is undiagnosed[1-3] may partly be attributed to the lack of an ideal screening method. A mass glaucoma screening method that is safe, specific, sensitive and acceptable to participants is needed. Recently, frequency-doubling technology (FDT) perimetry was shown to be an effective method for glaucoma screening[10, 11], but evaluating the optic disc or nerve fiber layer directly may be a preferable method to eliminate variability due to subjective judgment. Several novel digital imaging technologies[4-7] have been developed for the structural investigation of the optic nerve head. Scanning laser tomography, optical coherence tomography, and scanning laser polarimetry discriminated between glaucomatous and normal eyes with clinically useful sensitivities and specificities in hospital-based studies.[4-7] In addition, Harasymowycz et al[12] reported that HRT II using MRA or cup shape measurements may be a valid screening tool to detect clinically diagnosed glaucomatous optic nerve damage in high-risk populations. It was reported that measurement of optic disc parameters on stereoscopic fundus photographs was limited by difficulties in obtaining high quality photographs on all subjects, even if the pupils are dilated.[13] Recently, the digital nonmydriatic fundus camera was improved, and Dentry-Morel and colleagues[14] reported that a total of 98.1% of optic disc photographs taken by the non-mydriatic fundus camera could be interpreted and therefore could be a useful and quick method to screen for glaucomatous damage in a community. Furthermore, recent improvement in the digital nonmydriatic fundus camera enables stereo photographs of the optic disc to be taken without pupillary dilatation. In the present study, we evaluated the efficacy of HRT II scanning using MRA compared with nonmydriatic stereoscopic fundus photography in a population-based glaucoma screening.

Nonmydriatic stereoscopic photographs and HRT II scans were successfully obtained in the large majority of eyes (97.2% and 99.0%, respectively). Good quality photographs (enabling good stereopsis) were obtained in 93.4% of eyes by a nonmydriatic stereoscopic camera. Acceptable images (topographic standard deviation no greater than 50□m) were obtained in 91.9% of eyes by HRT II. These results were equal to HRT II in a population-based glaucoma screening for high-risk population (acceptable quality, 88%).[12] Therefore, both instruments were deemed acceptable for mass glaucoma screening.

HRT sensitivity and specificity were 72.6% and 89.7%, respectively, when “borderline” outcomes were treated as test positives (MRA 1) and 60.3% and 95.6%, respectively, when “borderline“ outcomes were treated as test negatives (MRA 2) for eye-level analysis. These results were similar to those reported by Ford et al[15], although the MRA of HRT II was based on data from white subjects while our study population was Japanese. As Vitale and colleagues[16] showed previously, at the personal level sensitivity increased and specificity decreased, relative to eye-level analysis. Indeed, in this study, HRT sensitivity increased without much impact on specificity when “borderline” outcomes were treated as test positives (MRA 1) at personal-level analysis. Although HRT was not sensitive enough for eye-level analysis, HRT might be useful for glaucoma screening for personal-level analysis.

Although the ratio of a good image obtained with nonmydriatic stereoscopy was 93.4%, that obtained for glaucoma was only 73.4%. By the same token, definite glaucoma was detected in 31.8% (21/66) of eyes in which stereoscopic photographs could not be interpreted. In other words, those eyes in which stereoscopic photographs could not be interpreted seemed to be a high risk group for glaucoma. Conversely, of the 23 eyes for which HRT II imaging data could not be obtained, definite glaucoma was diagnosed in only one eye (4.3%). In addition, of the 199 eyes for which acceptable images could not be obtained, definite glaucoma was diagnosed in 21 eyes (21/199, 10.6%). Therefore, detection number by HRT II (52/60) exceeded the detection number by stereoscopic photography (46/48) as long as interpretable photographs or images were obtained.

Most subjects with POAG (92.3%) had an IOP below 21 mmHg in the Tajimi study.[3] In our study, 86.2% (50/58) of all patients with POAG had an IOP below 21 mmHg and a single measurement of IOP detected only 3.3% of all glaucoma. A recent Japanese population study[3] reported the mean IOP of a Japanese population to be 14.6 mmHg ± 2.7 (standard deviation) in the right eye and 14.5 mmHg ± 2.7 in the left eye. Therefore, our cut-off IOP value in this study might be not appropriate. If the cut-off IOP value was 17mmHg or 19mmHg, the glaucoma detection rate using IOP was 18.3% (11/60) or 11.6% (7/60), respectively. Thus, our results are consistent with the conclusion of past reports that measurement of IOP alone is a poor tool to detect glaucoma.[14, 17, 18]

The estimated prevalence of POAG (5.1%) in this study appeared to be higher than that of a recent Japanese population-based glaucoma survey (3.9%).[3] This difference could be partly because our study population may have been biased by the use of volunteers, probable over-representation of subjects interested in glaucoma, and the older age of our subjects (61.6±10.5 years [mean ± standard deviation]) compared to the participants in the Japanese survey (58.4±11.8 years [mean ± standard deviation]).[3] Since the efficiency of screening methods was the main interest of our study, rather than estimation of the prevalence of glaucoma, a random sample of eligible participants was not requested.

In this study, there were several limitations due to the population-based and large-scale study. First, we did not perform definitive examinations of participants whose eyes appeared normal in the initial screening examinations. Subjects with glaucoma may therefore have been overlooked. In a recent Japanese population study[3], four out of 119 glaucoma patients were detected by FDT alone, suggesting that 3.4% (4/119) of glaucoma patients were overlooked by monoscopic fundus photography. In this study, we evaluated stereoscopic fundus photographs of optic discs to estimate vertical cup-to-disc ratio, which is reported to be more reliable than monoscopic evaluation.[19] However, we still cannot deny the possibility that we too overlooked a few glaucoma patients. Moreover, it is likely that obtaining a pair of images that enable a stereo view would fail, particularly in more elderly subjects.[13] In fact, in this study a total of 6.6% of the photographs did not enable a good stereo view, 10.7% of which were from subjects aged 70 years or older. Of 126 subjects where good quality photographs in at least one eye could not obtained, 71 subjects were judged to be normal by monoscopic fundus photography. The remaining 55 subjects were referred for a definitive examination and 14 were diagnosed as definite glaucoma. Therefore, it is unlikely that we overlooked considerable number of glaucoma.

Second, we could not perform definitive examinations on all subjects recruited for definitive examinations. However, there was no significant difference between the average age of subjects who had definitive examinations (61.4±10.4 years [mean ± standard deviation]) and those who did not (66.1±11.1 years [mean ± standard deviation]) ($P=0.083$, Student's t test). Also, the proportion of glaucoma patients in the group undergoing a definitive examination (23.9%, 60/251) was similar to that of the group that failed to attend the definitive examination (22.2%, 10/45) ($P=0.807$, chi-square test), in whom glaucoma was identified in the initial screening. Therefore, we think that this second limitation did not greatly influence the efficiency of HRT II in this screening.

Third, we performed visual field tests once and almost all the subjects were inexperienced in these tests. It was reported in an Ocular Hypertension Treatment Study[20] that most visual field abnormalities were not verified on retest so the reliability of the visual field test is limited. However, in definitive examinations we determined the final glaucoma diagnosis not only on visual field tests but also on disc appearance judged by a glaucoma specialist. Of the subjects classified as category 1, all fulfilled the rather conservative criteria of at least one abnormal hemifield and a compatible optic disc appearance, a nerve fiber layer defect, or both. Glaucoma subjects in category 2 may also include some preperimetric or suspected glaucoma patients even though more strict diagnostic criteria were applied to optic disc appearance.

This study showed that the use of nonmydriatic stereoscopic fundus photography and HRT II is a suitable approach for an initial glaucoma mass screening because images of both eyes can be rapidly acquired without the need for pupillary dilatation. This screening could conceivably be performed in the absence of a trained ophthalmologist and without pupillary dilatation. The evaluation of stereophotographs is subjective and test results clearly depend on the examiner's experience. In addition, good photographs were harder to obtain on glaucoma eyes than normal eyes, results that are similar to a Baltimore Eye Survey[13].

Compared with optic disc stereophotographs, HRT II provided objective and quantitative data and measurements were successful in almost all glaucomatous eyes. In this study, we defined regions of interest (ROIs) by drawing contour lines on stereoscopic photographs. However, if HRT II were to be used as a screening instrument, then disc photos would not be available. Watkins et al[21] reported no difference in the defined ROI when two experienced observers defined ROIs from stereoscopic or non-stereoscopic optic disc photographs, or without any photographic guide. Therefore, contour lines may be drawn with or without a photographic aid, and the results are unaffected. However, in this study, we used stereoscopic optic disc photographs to draw contour lines to reduce dependency on operator's skill.

In this study, costs associated with recruiting eligible subjects or management of contact information were negligible because this study was performed as part of a community health screening project. Personnel costs were $8765 while direct costs were almost $2600. Since we detected 54 new definite glaucoma patients, the estimated cost of the initial screening per new case was approximately $210. However, this does not include medical equipment.

Although HRT II did not detect glaucoma as well as optic nerve stereophotographs in this Japanese population, it may play a role in community health screening. Furthermore, HRT II retains the potential to increase the detection rate of glaucoma in conjunction with other diagnostic techniques such as FDT.

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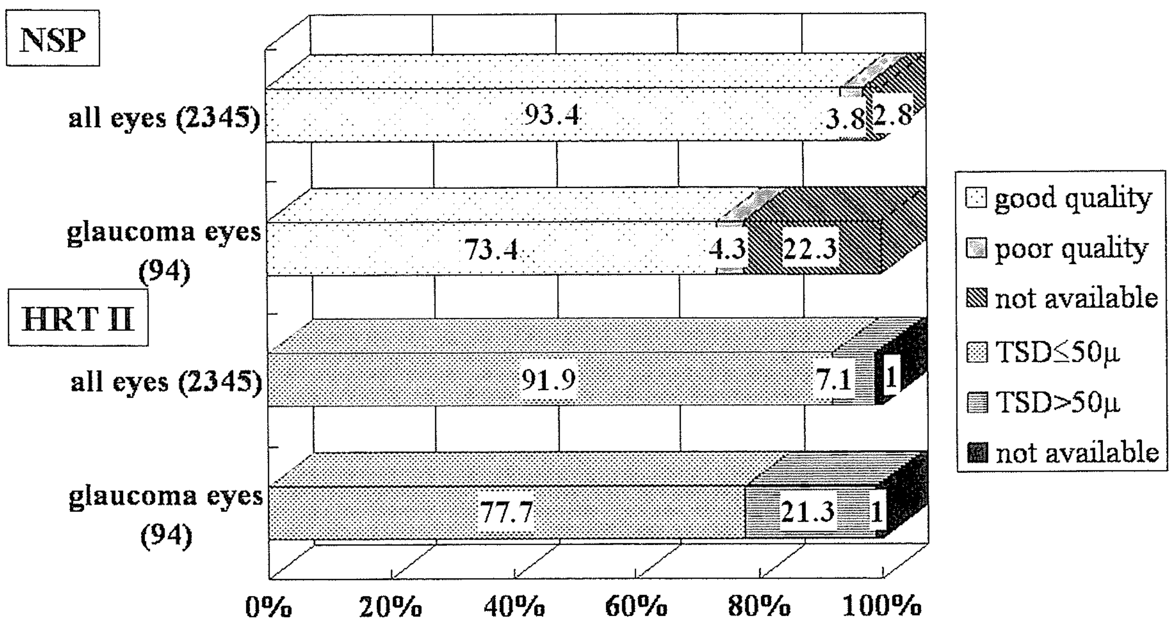
## Legends

**Figure 1.** Comparison of images acquired by nonmydriatic stereoscopic photography and Heidelberg Retina Tomography II for diagnosis. NSP = Nonmydriatic stereoscopic photography; HRT II = Heidelberg Retina Tomograph II, and TSD = Topographic standard deviation.

**Figure 2.** Distribution of Topographic standard deviation (TSD) of Heidelberg Retina Tomograph II in both eyes of all the subjects who participated.

**Figure 3.** Venn diagram showing the number of eyes which could not be interpreted by stereoscopic photography, or which could not be scanned by HRT II, or both.

**Figure 4.** Venn diagram showing the number of eyes which had poor quality stereoscopic photography, or unacceptable quality (above 50□m) HRT II, or both.



NSP
all eyes (2345)
93.4
3.8
2.8
glaucoma eyes (94)
73.4
4.3
22.3
HRT II
all eyes (2345)
91.9
7.1
1
glaucoma eyes (94)
77.7
21.3
1
0%
20%
40%
60%
80%
100%
good quality
poor quality
not available
TSD≤50μ
TSD>50μ
not available


Fig. 1

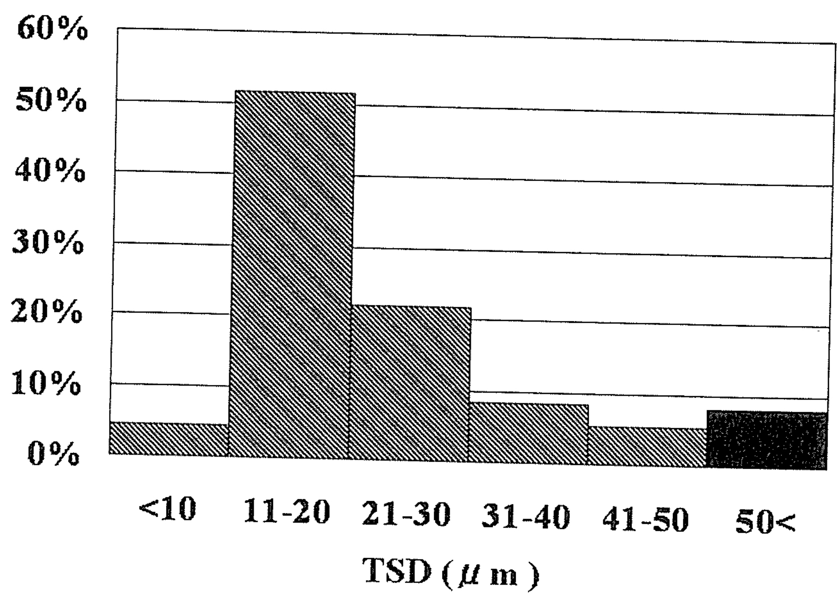



Fig. 2

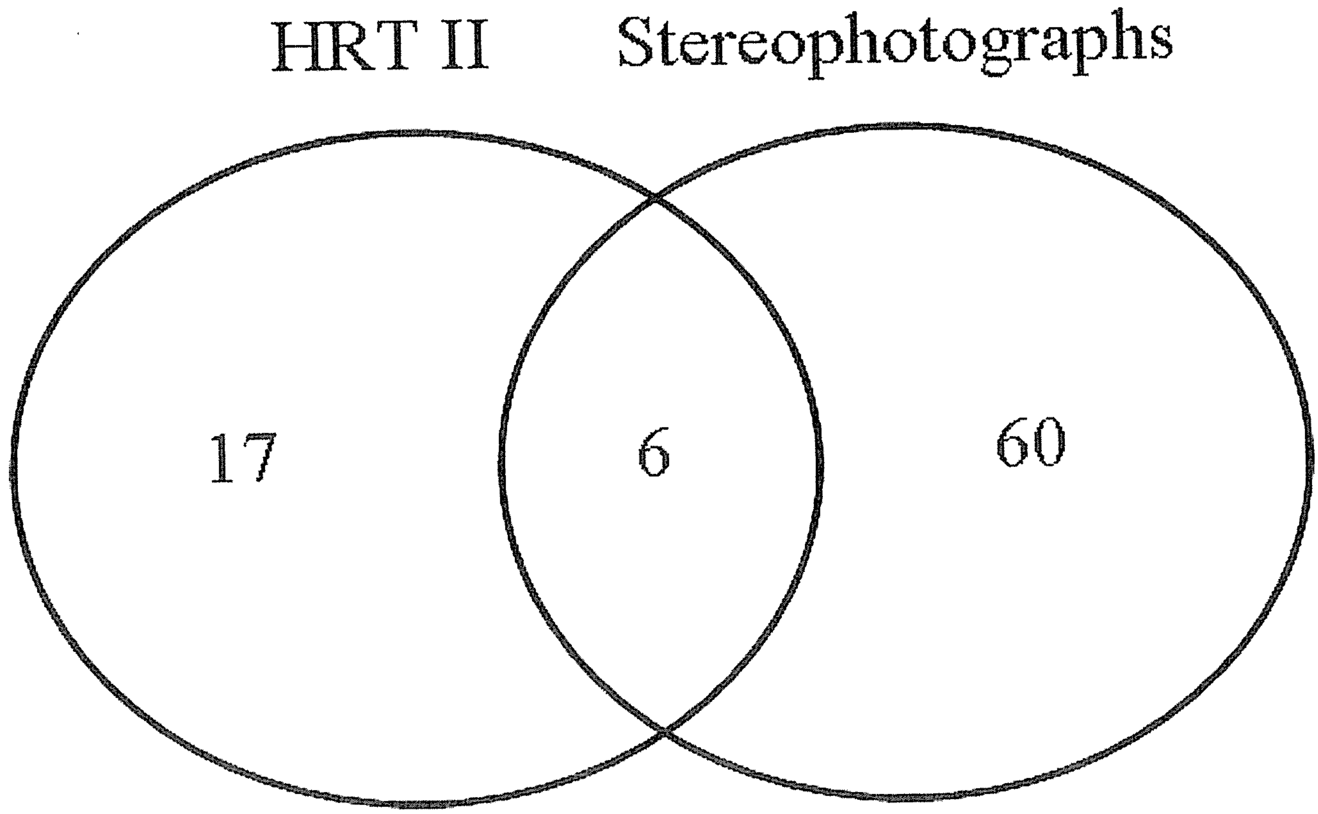



Fig. 3

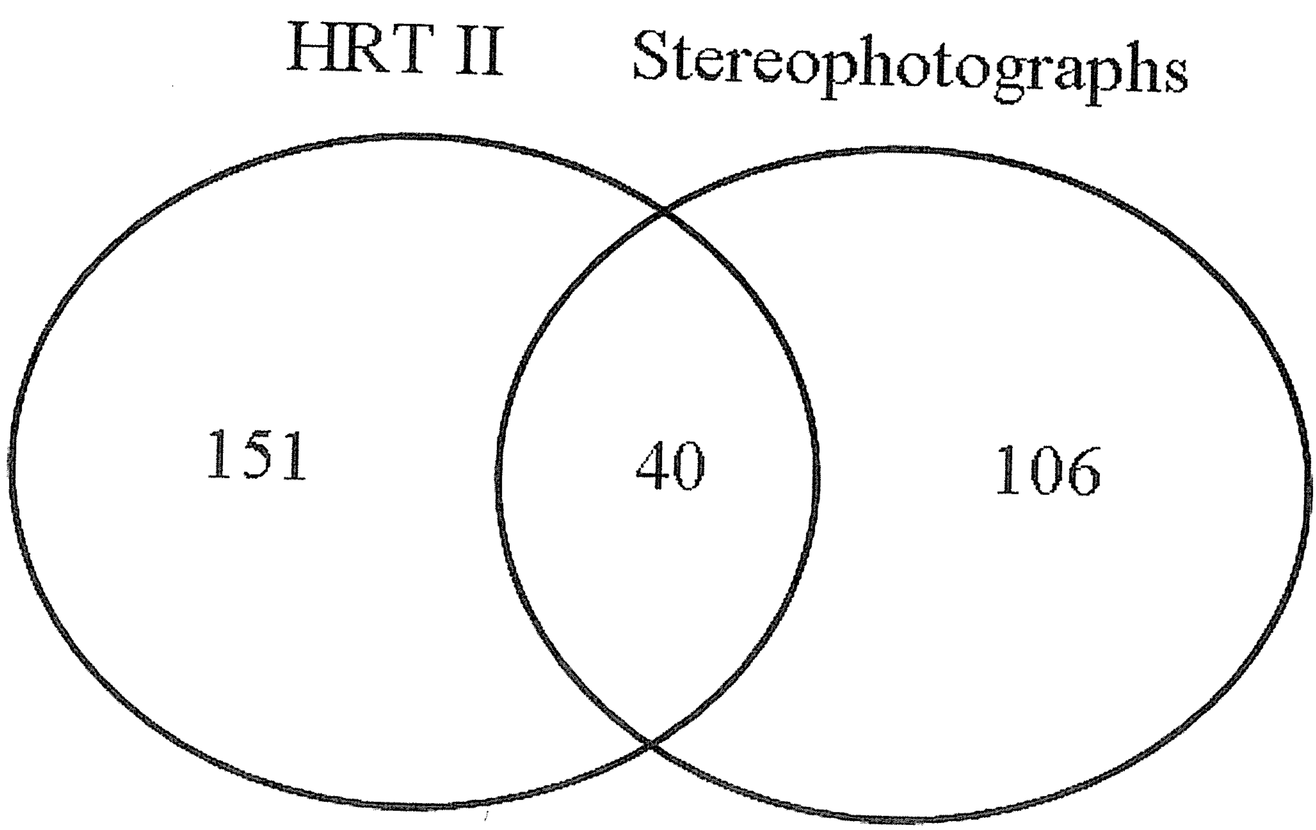





Fig 4

**TABLE 1**. The Criteria for Definitive Examination Eligibility

| | |
|---|---|
| 1) | Intraocular pressure of 21 mmHg or higher in either eye |
| 2) | Any findings suggesting the presence of abnormality including glaucomatous change (one or more of the following existed: the vertical cup/disc ratio of the optic nerve head was more than or equal to 0.6, the rim width at the superior portion (11-1 hour) or inferior portion (5-7 hour) was less than or equal to 0.2 of disc diameter, the difference in the vertical cup/disc ratio was more than or equal to 0.2 between both eyes, or a nerve fiber layer defect or splinter disc hemorrhage was found) as seen in stereoscopic fundus photographs |
| 3) | A "borderline" or "outside normal limits" classification as detected by HRT II |
| 4) | Failure to take stereoscopic fundus photographs or obtain HRT II images |

HRT II = Heidelberg Retina Tomograph II

TABLE 2. Prevalence Rate of Definitive Glaucoma in the Screened Population

| Age Groups (years) | Glaucoma (%; 95% Confidence Interval) | | |
|---|---|---|---|
| | Male | Female | All |
| 40-49 | 0/46 (0%, 0-0) | 3/113 (2.7%, -0.3-5.7 ) | 3/159 (1.9%, -0.2-4.0 ) |
| 50-59 | 2/91 (2.2%, -0.8-5.2 ) | 5/201 (2.5%, 0.3-4.7 ) | 7/292 (2.4%, 0.6-4.2 ) |
| 60-69 | 8/174 (4.6%, 1.5-7.7 ) | 10/236 (4.2%, 1.6-6.8 ) | 18/410 (4.4%, 2.4-6.4) |
| 70 and older | 13/103 (12.6%, 6.2-19.0) | 19/164 (11.6%, 6.7-16.5) | 32/267 (12.0%, 8.1-15.9 ) |
| All subjects | 23/414 (5.6%, 3.4-7.8 ) | 37/714 (5.2%, 3.6-6.8) | 60/1128 (5.3%, 4.0-6.6 ) |

**TABLE 3.** The Image Status of Each Instrument by Age

| Age Groups (years) | NSP | | | HRT II | | |
|---|---|---|---|---|---|---|
| | Good image eyes | Poor image eyes | Not available eyes | TSD≤50 μ | TSD>50 μ | Not available eyes |
| 40-49 | 321 (99.7%) | 0 (0%) | 1 (0.3%) | 310 (96.3%) | 11 (3.4%) | 1 (0.3%) |
| 50-59 | 577 (95.2%) | 20 (3.3%) | 9 (1.5%) | 585 (96.5%) | 16 (2.7%) | 5 (0.8%) |
| 60-69 | 785 (92.4%) | 46 (5.4%) | 19 (2.2%) | 785 (92.4%) | 62 (7.2%) | 3 (0.4%) |
| 70 and older | 506 (89.3%) | 24 (4.2%) | 37 (6.5%) | 474 (83.6%) | 79 (13.9%) | 14 (2.5%) |
| All subjects | 2189 (93.4%) | 90 (3.8%) | 66 (2.8%) | 2154 (91.9%) | 168 (7.2%) | 23 (0.9%) |

NSP = Nonmydriatic stereoscopic photography , HRT II = Heidelberg Retina Tomograph II; TSD = Topographic standard deviation