Glaucoma

Rates of Glaucomatous Visual Field Change in a Large Clinical Population

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PURPOSE. To determine the rate of glaucomatous visual field change in routine clinical care.

METHODS. Mean deviation (MD) rate was computed in one randomly selected eye of all glaucoma patients and suspects with ≥ 5 examinations in a tertiary eye-care center. Proportions of "fast" (MD rate, < -1 to -2 dB/y) and "catastrophic" (< -2 dB/y) progressors were determined. The MD rates were computed in tertile groups by the number of examinations, baseline age, and MD. The MD rates were compared to the Canadian Glaucoma Study (CGS), a prospective study with IOP interventions mandated by visual field progression, by pairwise matching of patients by baseline MD.

RESULTS. There were 2324 patients with median (interquartile range) baseline age and MD of 65 (56, 74) years and -2.44 (-5.44, -0.86) dB, and follow-up of 7.1 (4.8, 10.2) years with 8 (6, 11) examinations. The median MD rate was -0.05 (0.13, -0.30) dB/y, while the mean follow-up IOP was 17.1 (15.0, 19.7) mm Hg. The MD rate was progressively worse, with a doubling of fast and catastrophic progressors, with each tertile of increasing age. Worse MD rate was associated with lower follow-up IOP. Neither MD rate nor the number of fast and catastrophic progressors was significantly different in clinical care patients matched to CGS patients.

CONCLUSIONS. Most patients under routine glaucoma care demonstrate slow rates of visual field progression. The MD rate in the current study was similar to an interventional prospective study, but considerably less negative compared to published studies with similar design.

Keywords: glaucoma, visual field, progression, clinical study

Clinical trials and longitudinal studies in glaucoma have provided important data on the incidence of visual field progression.[1–9] However, the incidence of progression, defined as a binary outcome (progression or no progression), depends entirely on the criteria used to define it. Since there is little standardization of these criteria or their veracity, it is challenging to compare the number of patients with visual field progression among these studies. Furthermore, whether progression occurs may have different clinical consequences depending on the age and level of visual field loss. For example, progression in a 90-year-old patient with early damage has different implications compared to a 50-year-old with advanced damage.

Determining the rate of visual field change overcomes some of the limitations of the arbitrary event-based criteria for progression. Direct comparisons of rates of change between studies can be made. In individual patients, the rate of visual field change allows the clinician to prognosticate the likelihood of lifetime visual disability by taking into account factors, such as age, life expectancy, and the amount of presenting visual field loss.

Numerous reports have estimated that the average rate of visual field change, defined as the mean deviation (MD) rate, in glaucoma patients ranges from 0 to -1.1 dB/y.[5,6,10–21] Because these figures are derived from patients in prospective studies, it is conceivable that corresponding rates in patients not enrolled in studies could be worse because study subjects may be more adherent to treatment and less likely to be lost to follow-up. Indeed, Henson and Shambhu[22] showed that nonstudy patients matched to study patients for the amount of visual field loss and length of follow-up had a higher incidence of visual field progression. More recently, Heijl et al.[23] reported a median MD rate of -0.62 dB/y in patients undergoing routine care.

The purpose of the current study was to determine the distribution of MD rate in a large group of patients, not enrolled in studies, receiving routine clinical care. Additionally, we wanted to determine whether MD rates in subsets of these patients were different to those matched pairwise the amount of visual field loss in the Canadian Glaucoma Study (CGS), an interventional prospective study,[24] and a similar study by Heijl et al.[23]

METHODS

Patients

All glaucoma patients and suspects followed for routine clinical care in the Eye Care Centre of the Queen Elizabeth II Health Sciences Centre and one satellite clinic were included. Patients enrolled in research studies were excluded. Capital Health Ethics Review Board approval was obtained.
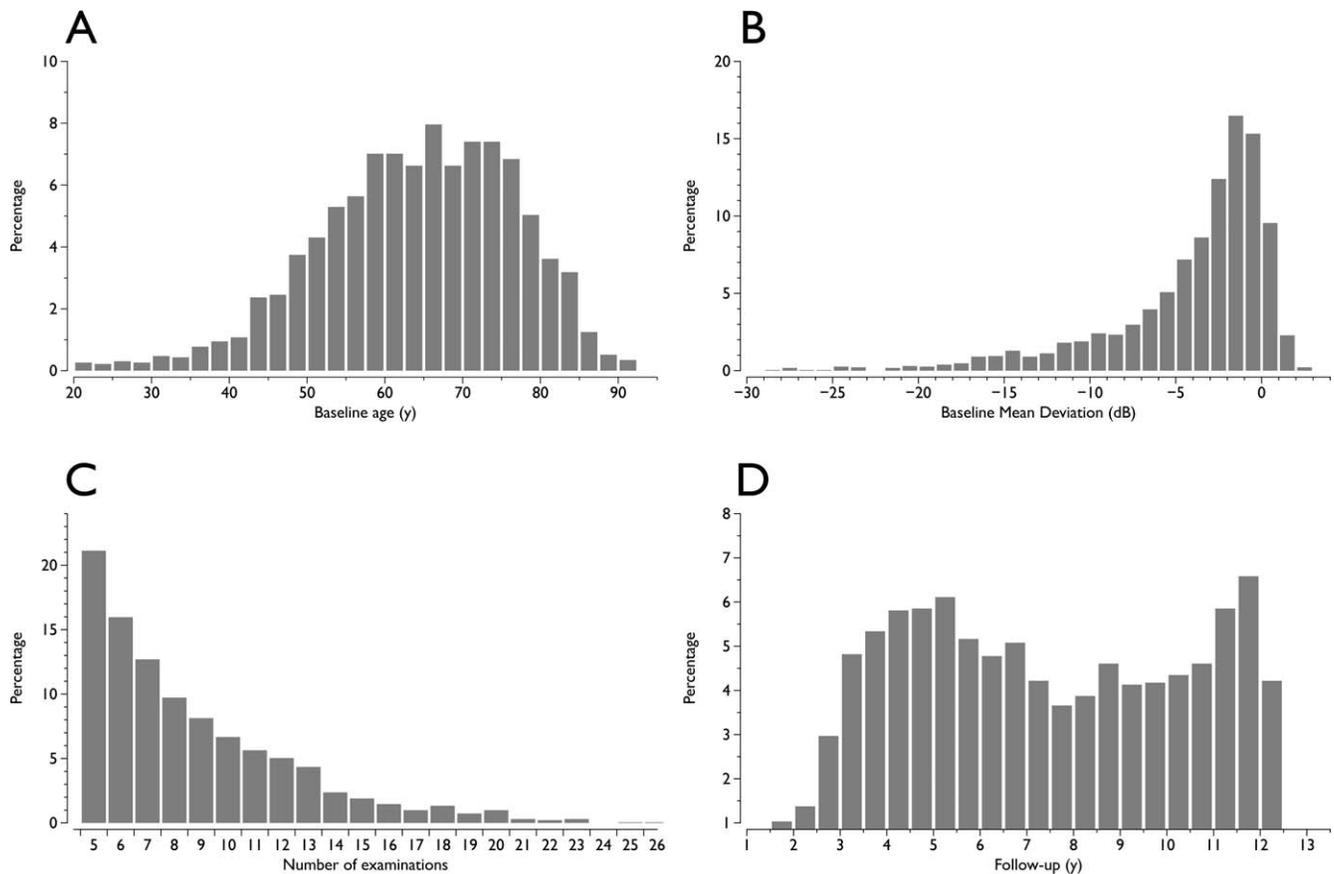
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Figure 1. Distribution of baseline age (**A**), baseline MD (**B**), number of visual field examinations (**C**), and the follow-up time (**D**) in all 2324 patients in the study.

The described research adhered to the tenets of the Declaration of Helsinki.

Data Selection

From the entire dataset containing visual fields obtained with the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA), those patients with ≥5 visual field examinations with the Swedish Interactive Thresholding Algorithm (SITA) standard 24-2 program were selected. If both eyes were eligible, one was selected randomly for analysis. The IOP on the day of each perimetric examination was extracted from the records.

Data Analysis

Perimetric data were exported with external software (Peri-Data, Huerth, Germany) and analysis was performed with the open-source R program (R Development Core Team, Vienna, Austria) and SPSS Statistics (version 20; IBM, Armonk, NY, USA).

The MD rate for each subject was computed with robust regression,[25] a technique that provides slope estimates more resistant to outlier observations compared to ordinary least squares regression. The proportion of fast and catastrophic progressors, defined respectively as patients with MD rates of <−1 to −2 dB/y, and <−2 dB/y, was computed. Patients were divided into three similarly sized (tertile) groups by number of visual field examinations, baseline MD, and baseline age.

Correlation and multiple regression analyses were conducted on baseline and follow-up factors associated with MD rate.

Patients from two different studies then were matched pairwise to those from the current one by baseline MD to determine whether MD rates in patients in a closely monitored interventional prospective study[24] were different from those in the current study and to compare MD rates in a similar routine clinical care study.[23] Baseline age, baseline MD, mean follow-up IOP, and MD rate were obtained from the CGS, described previously in detail.[24] Briefly, patients were followed with perimetry every 4 months and those with a repeatable end-point were mandated to receive ≥20% IOP reduction in IOP. Further end-points each required additional ≥20% IOP reduction. Only those patients with ≥5 visual field examinations were selected. The MD rate was calculated for the entire follow-up, irrespective of the number of end-points. Thus, CGS patients were followed closely with perimetry and whose treatment interventions were based on visual field changes. Baseline age, baseline MD, mean follow-up IOP, and MD rate also were obtained from a recent study by Heijl et al.[23] that had a design similar to that of the current study. Baseline MD for the patients in the study of Heijl et al.[23] was derived from Figure 1 (rounded to the nearest 2 dB) in their publication. A computer program selected patient pairs with the least MD difference from all possible candidate matches with the condition that each patient's data could be used only once. The proportion of fast and catastrophic progressors among the paired groups was computed and compared with the χ^2 test, while the MD rates were compared with the Wilcoxon test.

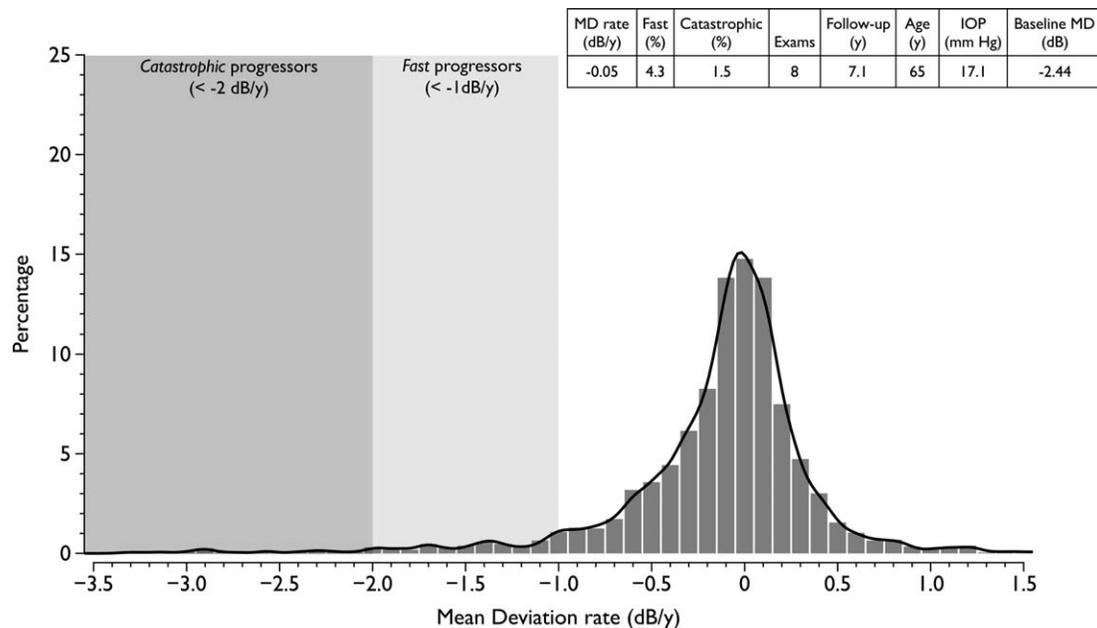| MD rate (dB/y)	Fast (%)	Catastrophic (%)	Exams	Follow-up (y)	Age (y)	IOP (mm Hg)	Baseline MD (dB)
-0.05	4.3	1.5	8	7.1	65	17.1	-2.44

FIGURE 2. Distribution of MD rate in all 2324 patients in the study. Also shown are medians for MD rate, number of examinations, follow-up, baseline age, mean follow-up IOP, baseline MD, and the proportion of fast and catastrophic progressors. *Curved line* represents a spline fit of the histogram.

RESULTS

The total material consisted of 20,189 eyes of 10,385 patients with 65,460 visual field examinations. Of these, one eye of 2324 (22%) patients had ≥ 5 examinations (total, 20,138 [31%] examinations) and selected for analysis. Of these, IOP data were available in 1948 (84%) patients.

The median (interquartile range [IQR]) and mean (SD) baseline age, and baseline MD were 65 (56, 74) and 64 (13) years, and −2.44 (−5.44, −0.86) and −4.01 (4.75) dB, respectively (Fig. 1). The median (IQR) and mean (SD) follow-up and number of examinations were 7.1 (4.8, 10.2) and 7.4 (3.0) years, and 8 (6, 11) and 8.7 (3.7), respectively (Fig. 1).

The overall distribution of MD rate is shown in Figure 2. The median (IQR) and mean (SD) values were −0.05 (0.13, −0.30) and −0.15 (0.78) dB/y, respectively. There were 99 (4.3%) patients with fast and 34 (1.5%) patents with catastrophic progression. The median (IQR) mean follow-up IOP was 17.1 (15.0, 19.7) mm Hg, while the maximum and minimum follow-up IOP was 21.0 (18.0, 24.0) and 14.0 (12.0, 16.0) mm Hg, respectively. Sectoral[26] MD rates (Supplementary Fig. S1) had similar median values.

The median MD rate was very similar among the tertile groups by the number of examinations (Fig. 3); however, the proportion of fast and catastrophic progressors decreased with an increasing number of examinations (Fig. 3). Expectedly, the respective median follow-up increased with each tertile (medians, 4.7, 7.3, and 8.3 years, respectively). However, the annual frequency of examinations was similar (medians, 1.2, 1.1, and 1.3 examinations/y, respectively). Among the tertiles by baseline MD, the proportion of fast and catastrophic progressors was notably higher in last tertile (median baseline MD, −7.79 dB) compared to the other two tertiles (Fig. 4). Finally, among the tertile groups by baseline age, there was a progressive worsening of MD rate with each age increment (Fig. 5). The median MD rate was 0.03 dB/y in those patients with a median baseline age of 52 years compared to −0.17 dB/y

in those with a median baseline age of 77 years. The proportion of fast and catastrophic progressors increased by a factor of 2 with each age increment (Fig. 5).

The MD rate was not correlated with baseline MD (Spearman's $\rho = 0.04$, $P = 0.09$, Fig. 6), but was worse with higher baseline age ($\rho = -0.27$, $P < 0.01$, Fig. 6), lower mean follow-up IOP ($\rho = 0.15$, $P < 0.01$, Fig. 6), and higher range of follow-up IOP ($\rho = 0.12$, $P < 0.01$). The MD rate also was positively correlated with the rate of change in IOP over follow-up time ($\rho = 0.11$, $P < 0.01$). In multiple regression analysis, baseline age and range of follow-up IOP were significant ($P < 0.01$) factors affecting MD rate; however, mean baseline MD, mean follow-up IOP, and the number of examinations were not ($P > 0.29$). While the model fit was statistically significant ($P < 0.01$), it yielded an R^2 of only 0.03, indicating that the independent variables explained only 3% of the variation in MD rate.

All 225 patients in the CGS were matched successfully pairwise to patients in the current study by baseline MD. The median signed and absolute paired difference in baseline MD was 0.00 dB. The MD rate in the matched patients was not significantly different (median paired difference, 0.01 dB/y, $P = 0.35$, Fig. 7). However, there was a nonsignificantly higher proportion of fast and catastrophic progressors in the current study ($P = 0.21$, Fig. 7). The baseline age in the matched patients was similar ($P = 0.10$); however, the mean follow-up IOP in the CGS was significantly lower compared to the current study (respective medians, 16.4 and 17.3 mm Hg, $P = 0.03$) and the follow-up was significantly shorter (respective medians, 6.2 and 6.9 years, $P < 0.01$).

The MD rate in the patients in the current study matched by baseline MD to those of Heijl et al.[23] was more positive (medians, −0.11 and −0.62 dB/y, respectively, Fig. 8). There also were almost 4 times more fast progressors and over 3 times more catastrophic progressors in the study of Heijl et al.[23] compared to the current study ($P < 0.01$, Fig. 8). The mean follow-up IOP in the study of Heijl et al.[23] (20.2–18.1 mm Hg) was higher compared to matched patients in the current study

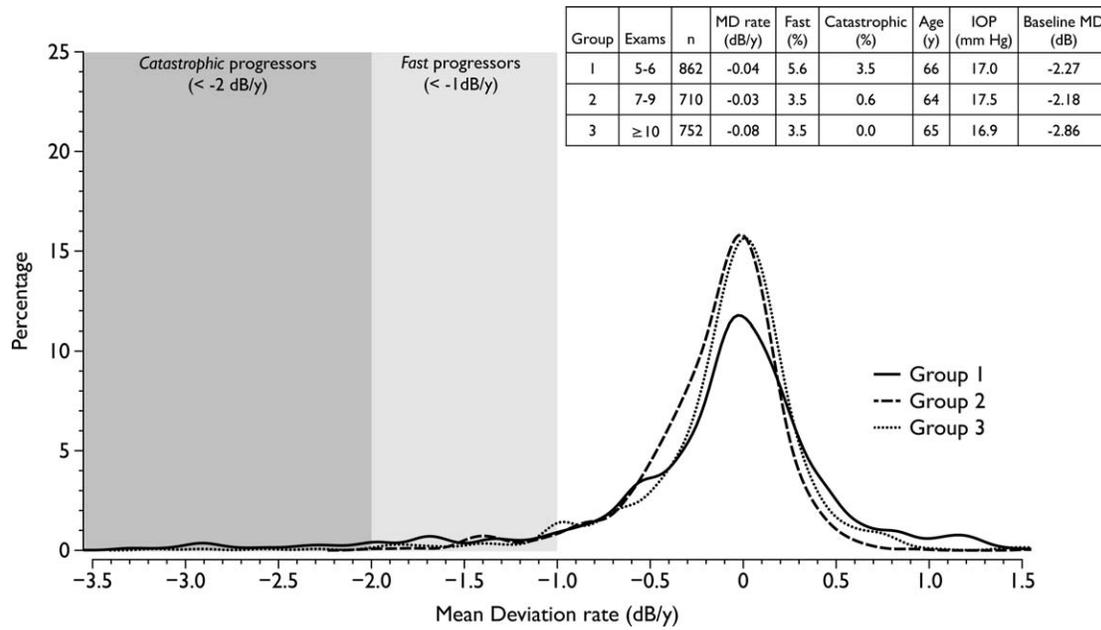| Group	Exams	n	MD rate (dB/y)	Fast (%)	Catastrophic (%)	Age (y)	IOP (mm Hg)	Baseline MD (dB)
1	5-6	862	-0.04	5.6	3.5	66	17.0	-2.27
2	7-9	710	-0.03	3.5	0.6	64	17.5	-2.18
3	≥10	752	-0.08	3.5	0.0	65	16.9	-2.86

FIGURE 3. Distribution (spline fit of histogram) of MD rate in tertile groups based on the number of follow-up examinations. Also shown are number of patients in each group, medians for MD rate, baseline age, mean follow-up IOP, baseline MD, and the proportion of fast and catastrophic progressors.

(15.9 mm Hg). However, the baseline age was higher (means, 71 and 67 years, respectively) and the follow-up longer (means, 7.8 and 7.0 years, respectively) in the study of Heijl et al.[23] compared to the current study. Formal statistical comparisons require raw data from the study of Heijl et al.[23] and, therefore, with the exception of a comparison of fast and catastrophic progressors, these could not be performed. In multiple regression analyses of the matched patients in the current study, age (coefficient, −0.008/y, $P < 0.01$) was statistically

significantly associated with MD rate, while baseline MD, mean follow-up IOP, and follow-up duration were not ($P > 0.20$).

DISCUSSION

In this study, we purposely included the whole population of patients followed for routine clinical care, as long as they had ≥5 visual field examinations. We did not segregate the population into suspect and manifest cases with arbitrary
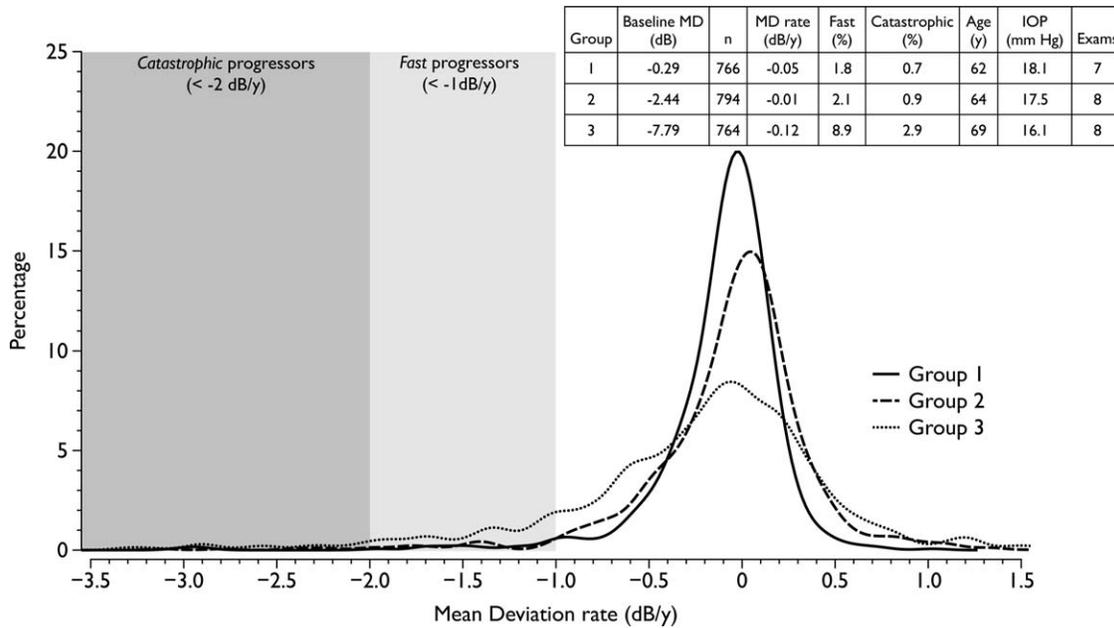

Group	Baseline MD (dB)	n	MD rate (dB/y)	Fast (%)	Catastrophic (%)	Age (y)	IOP (mm Hg)	Exams
1	-0.29	766	-0.05	1.8	0.7	62	18.1	7
2	-2.44	794	-0.01	2.1	0.9	64	17.5	8
3	-7.79	764	-0.12	8.9	2.9	69	16.1	8

FIGURE 4. Distribution (spline fit of histogram) of MD rate in tertile groups based baseline MD. Also shown are number of patients and visual field examinations in each group, medians for baseline MD, MD rate, baseline age, mean follow-up IOP, and the proportion of fast and catastrophic progressors.
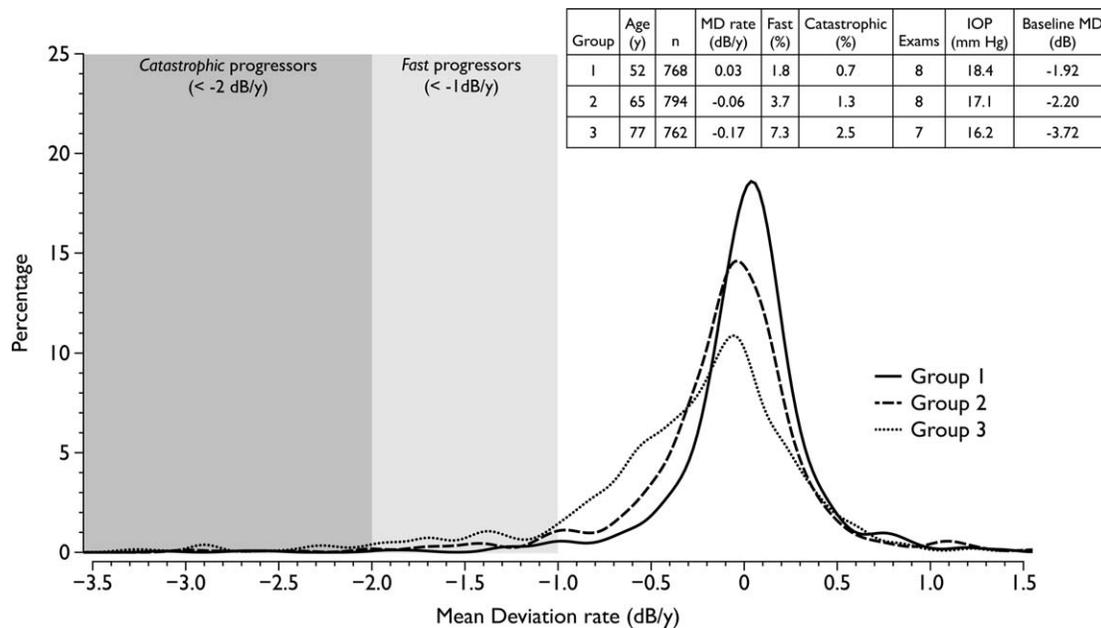
Group	Age (y)	n	MD rate (dB/y)	Fast (%)	Catastrophic (%)	Exams	IOP (mm Hg)	Baseline MD (dB)
1	52	768	0.03	1.8	0.7	8	18.4	-1.92
2	65	794	-0.06	3.7	1.3	8	17.1	-2.20
3	77	762	-0.17	7.3	2.5	7	16.2	-3.72

FIGURE 5. Distribution (spline fit of histogram) of MD rate in tertile groups based on baseline age. Also shown are number of patients and visual field examinations in each group, medians for baseline age, MD rate, baseline age, mean follow-up IOP, baseline MD, and the proportion of fast and catastrophic progressors.

clinical or perimetric criteria or apply other exclusion criteria, as we wanted to determine the rate of visual field change in the entire population. However, we provide segregated analysis on the basis of the number of examinations, baseline visual field damage, and age, as well as a pairwise matched analysis with a prospective interventional study and a study with a similar design.

On average, patients progressed slowly under routine clinical care. However, 4.3% of patients had fast (MD rate < −1 to −2 dB/y) and 1.5% had catastrophic (MD rate < −2 dB/y) progression. Assuming that significant visual field disability occurs at −25 dB, a patient with baseline MD of −5 dB would become visually disabled in 20 years with fast, and in 10 years with catastrophic progression. While there are important caveats in assuming that an arbitrary value of MD (which does not discriminate central from mid-peripheral visual field loss) represents visual disability, such approximations allow clinicians to estimate the likelihood of visual disability during a patient's lifetime, taking into account baseline age, baseline MD, life expectancy, and MD rate. Such approximations also are helpful in planning the frequency of visual field testing in individual patients.[27] We elected to use MD and not the Visual Field Index (VFI),[28] because of the ceiling effect in the VFI and potential loss of sensitivity due to its reliance on pattern deviation values.[29] Furthermore, because the VFI resorts to total deviation when MD is approximately −20 dB, there are abrupt changes in its value,[30,31] rendering it less appropriate for computing the rate of visual field loss.

The precision of MD rate is related to several factors, including the length of follow-up and number of examinations. While the median MD rate was similar among the tertile groups by the number of examinations, the number of fast and catastrophic progressors decreased with each tertile. There also was a higher frequency of positive MD rates (>0.5 dB/y) with fewer examinations. These observations suggested that MD rates estimated from fewer examinations are relatively imprecise, resulting in more outlier observations.

Worse MD rate was associated with older baseline age, lower mean follow-up IOP, and a higher range of IOP during follow-up. In multiple regression analyses, however, the effects of mean follow-up IOP were explained by the range of follow-up IOP. Older age has been associated with a higher incidence or faster rate of progression,[5,7,32–34] though not universally.[35] In tertile groups by baseline age, there was a clear worsening of MD rate, and proportion of fast and catastrophic progressors with each age increment, supporting the notion that increased age exerts a strong independent effect on MD rate.

Our finding of worse MD rate with lower mean follow-up IOP is in disagreement with previous retrospective studies.[12,15] Inference on causality of follow-up IOP on progression cannot be made in studies not accounting for IOP interventions,[36] since the mean and range of follow-up IOP is affected by each intervention. The most plausible explanation for our findings is that patients with faster progression have more aggressive IOP reduction and, therefore, achieve a lower mean and higher range of follow-up IOP.

Determining the rate of visual field change in clinical settings[22,23,37,38] is important as rates derived from prospective studies or clinical trials may contain bias; for example, better adherence to IOP-reducing therapy[22] and regular visual field examinations, leading to more optimal care. Henson and Shambhu[22] showed that for each criterion for progression based on MD rate, patients enrolled in studies had a lower incidence of progression compared to those under routine clinical care. In the current study, there was no difference in MD rate between CGS patients matched to patients under routine clinical care by baseline MD. The sharp contrast between these two paired studies may be due to differences in study design. In the study of Henson and Shambhu,[22] pairwise matching was performed by baseline MD (maximum allowable pairwise difference, 3 dB), baseline pattern standard deviation, and follow-up duration, while in the current study it was done by baseline MD only with a much smaller paired difference (median signed and absolute value, 0.00 dB). The duration of follow-up of patients in the study of Henson and Shambhu[22] was approximately half of that in current study.

The finding of similar MD rates in CGS patients and clinical care patients has some important implications. Treatment
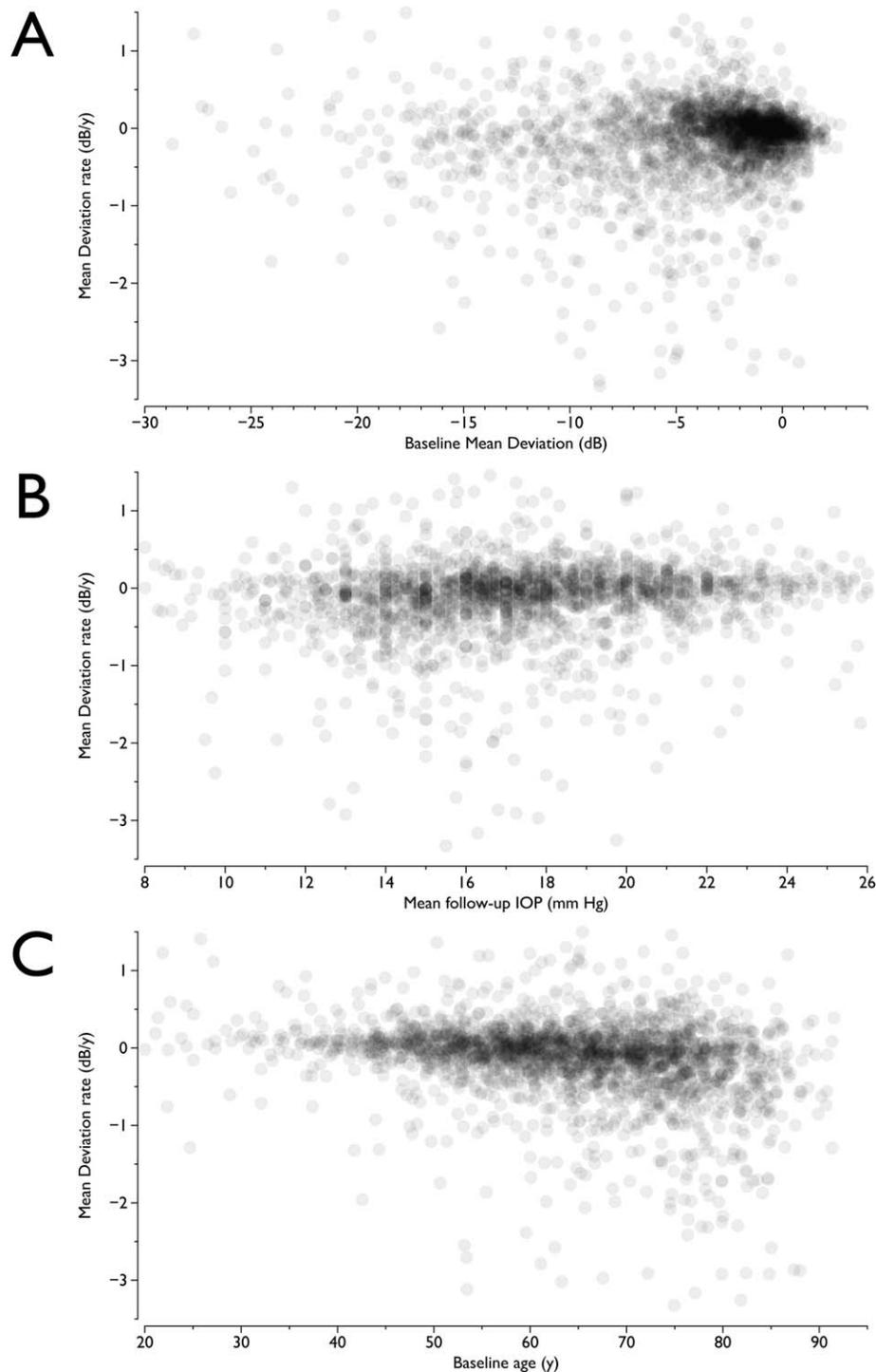
FIGURE 6. Scattergrams of MD rate and baseline MD (**A**), mean follow-up IOP (**B**), and baseline age (**C**).

interventions and target IOP in the CGS were determined by visual field progression and not on optic nerve changes or level of IOP, suggesting that similar decision rules were followed in this cohort of clinical care patients.

Studies on rates of visual field change in clinical populations have been conducted in the United States[37] and Sweden.[23] In their study of 587 patients with mean baseline MD of −7.1 dB/ y, mean age of 65 years, and mean follow-up IOP of 15.2 mm Hg, De Moraes et al.,[37] reported the rate of mean sensitivity loss of −0.45 dB/y. Unlike MD, mean sensitivity is not adjusted

for age, but after accounting for age-related sensitivity loss,[39,40] the equivalent MD rate would be approximately −0.35 dB/y. In their study of 583 patients, with a median baseline MD of −10 dB, mean age of 71 years, and mean follow-up IOP between 20.2 and 18.1 mm Hg, Heijl et al.[23] reported median and mean MD rates of −0.62 and −0.80 dB/y. In the tertile group with the most damaged visual fields at baseline in our study (median MD, −7.79 dB, similar to the results of De Moraes et al.[37] and Heijl et al.[23]), the MD rate was less negative (median and mean, −0.12 and −0.21 dB/y, respectively).

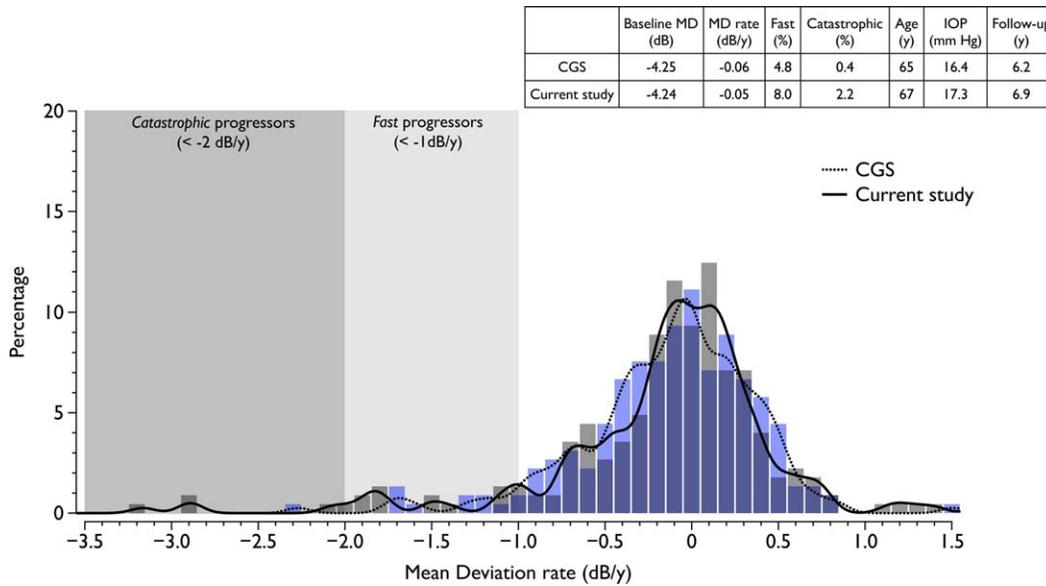|	Baseline MD (dB)	MD rate (dB/y)	Fast (%)	Catastrophic (%)	Age (y)	IOP (mm Hg)	Follow-up (y)
CGS	-4.25	-0.06	4.8	0.4	65	16.4	6.2
Current study	-4.24	-0.05	8.0	2.2	67	17.3	6.9

FIGURE 7. Distribution of MD rate in 225 patients in the CGS[24] (*blue bars*) and 225 patients in the current study (*gray bars*) matched pairwise by baseline MD. Also shown are medians for baseline MD, MD rate, baseline age, mean follow-up IOP, follow-up, and the proportion of fast and catastrophic progressors. *Curved lines* represent spline fit of the histograms.

De Moraes et al.[37] and Heijl et al.[23] found a relationship between higher mean follow-up IOP and worse MD rate. In the former study, the effects of follow-up IOP were explained by peak IOP analysis. These findings are in contrast with the current study, where lower mean follow-up IOP was associated with worse MD rate (explained by range of follow-up IOP). As indicated above, a lower mean follow-up IOP could be expected in faster progressing patients if visual fields were used as the basis of treatment interventions. The use of alternative or additional information from imaging of the optic nerve head and nerve fiber layer, or the level of IOP itself to

drive treatment decisions also could weaken the relationship and explain the worse MD rate.

The differences in MD rate in the study of Heijl et al.[23] and the matched patients in the current study are notable. Heijl et al.[23] reported group mean IOP from 20.2 to 18.1 mm Hg. These values are not equivalent to mean follow-up IOP in individual patients, but provide a fair approximation and indicate values between 2.2 and 4.3 mm Hg higher in the study of Heijl et al.[23] compared to the matched patients in the current study and is likely one source of the MD rate differences. In their multiple regression analyses,[23] age and
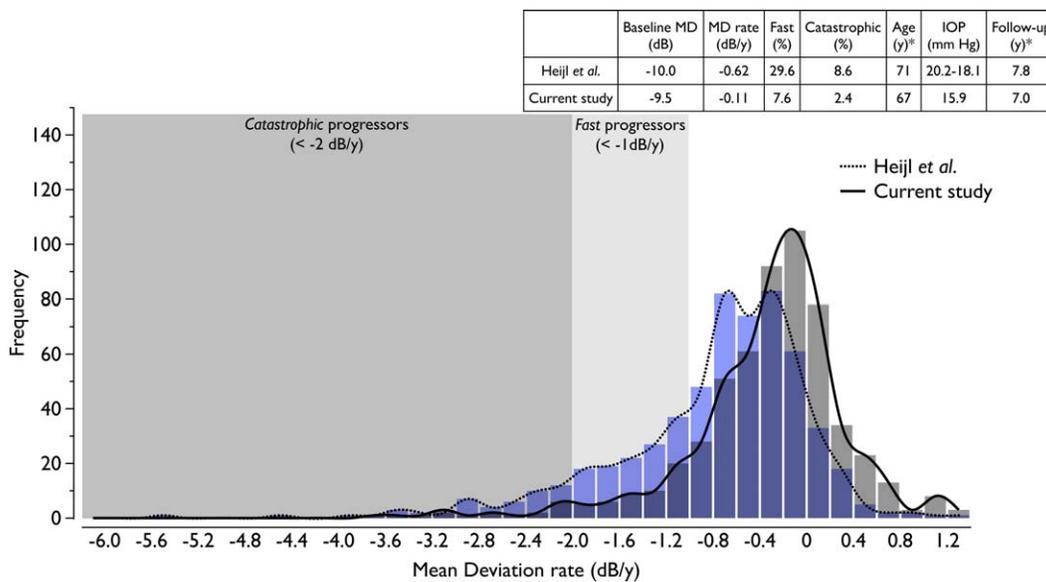
	Baseline MD (dB)	MD rate (dB/y)	Fast (%)	Catastrophic (%)	Age (y)*	IOP (mm Hg)	Follow-up (y)*
Heijl et al.	-10.0	-0.62	29.6	8.6	71	20.2-18.1	7.8
Current study	-9.5	-0.11	7.6	2.4	67	15.9	7.0

FIGURE 8. Distribution of MD rate in 583 patients in the study of Heijl et al.[23] (*blue bars*) and 583 patients in the current study (*gray bars*) matched pairwise by baseline MD. Also shown are medians for baseline MD, MD rate, and the proportion of fast and catastrophic progressors. Baseline age and follow-up are reported as means (*), since median values were not available in the study of Heijl et al.[23] The range of annual mean follow-up IOP is shown for the study of Heijl et al.,[23] while the median follow-up IOP is shown for the current study.

mean IOP were significant independent variables associated with MD rate, with coefficients of –0.019/y and –0.036/mm Hg, while in the current study only age, with a coefficient of –0.008/y, was significant. Hence, the difference in age and follow-up IOP between the two studies could statistically account for only 0.1 to 0.2 dB/y of the 0.5 dB/y observed difference in the median MD rate. Decision rules dictating treatment decisions, as discussed above, could be another source of the difference. Because of the nature of these studies, it was not possible to retrieve concurrent systemic disease or systemic medication use. Hence, differences in either of these factors also may have contributed to the observed differences. Similarly, patients in these two studies may have had different risk profiles, for example, higher untreated baseline IOP. Clinicians in the current study may have used lower target IOP resulting in a less negative MD rate.

There are several important limitations of the current study. Because of its retrospective nature, potentially important information, such as the presence of systemic disease and systemic medication use, was not available. Follow-up IOP data were missing in approximately 16% of the patients. Patients were treated by several ophthalmologists with nonstandardized protocols for IOP intervention and follow-up frequency, which while providing an accurate reflection of routine clinical care, likely introduces variability in MD rate.

In conclusion, in a large group of patients, not enrolled in research studies and followed for routine glaucoma care, we found the average rate of visual field change to be slow. We were unable to demonstrate meaningful differences in MD rates between these patients and those in a prospective interventional study, after matching patients pairwise for the amount of visual field loss. Finally, after matching patients to those from a recent study with similar design,[23] the MD rates in the current study were significantly less negative.

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