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# Smoking Cessation May Reduce Risk of Visual Field Progression in Heavy Smokers

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## Abstract

**Purpose:** To investigate the effect of smoking cessation on visual field (VF) progression in glaucoma.

**Patients and Methods:** Primary open-angle glaucoma patients with a minimum of 3 years follow-up and 5 visual fields (VF) were included. Linear mixed models were used to investigate the effects of smoking on the rates of 24–2 VF mean deviation loss after adjusting for confounding factors. Cox proportional hazard regression was used to identify whether different levels of smoking intensity were associated with VF progression with respect to different duration of quitting.

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**Concept and design:** Moghimi, Weinreb, Mahmoudinezhad,Nishida.

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**Results:** 511 eyes of 354 patients were included over the mean follow-up of 12.4 years. Mean baseline age (95%CI) was 62.3 (61.2,63.4) years. 168 (59.8%) patients were smokers. In a multivariable model, smoking intensity was associated with faster VF loss (−0.06, 95%CI (−0.10,−0.01) dB/year per 10 pack-years, P=0.01) among smokers. Heavy smokers (≥20 pack-years) who had quit less than 25 years prior had significantly greater odds of VF progression compared to never smokers (OR=2.49(1.01,6.08); P=0.046). There was no significant difference in odds of VF progression in heavy smokers who had quit smoking more than 25 years compared to never smokers (P=0.43). A significantly higher proportion of VF progression was found in heavy smokers who quit < 25 years compared to heavy smokers who quit≥25 years by Kaplan-Meier analysis (P=<0.001).

**Conclusions:** After ≥25 years of smoking cessation, the risk of VF progression in former heavy smokers becomes similar to never smokers. Long-term smoking cessation may be associated with lower VF progression in glaucoma patients.

## Précis

The earlier a person quits smoking the more likely is the optic nerve be spared from damage.

### Keywords

Primary open-angle glaucoma; Visual field; Smoking; Cessation

## Introduction

Glaucoma is a progressive optic neuropathy characterized by retinal ganglion cell degeneration and associated visual field (VF) damage.[1] Given the chronic, progressive, and irreversible nature of glaucoma, understanding risk factors is critically important.[2] Elevated intraocular pressure (IOP) is currently the only modifiable risk factor for glaucoma. Demographic factors (also known as non-modifiable or inherent determinants) such as older age[3] and African American race are related to the prevalence of glaucoma.[4]

Considerable interest exists in preventive measures other than IOP lowering for reducing the risk of glaucomatous optic nerve damage and visual field loss development and progression. Emerging research indicates that modifiable factors besides IOP including socioeconomic status (SES), nutritional intake, body mass index (BMI) and obesity, exercise, smoking, and sleep apnea may be associated with glaucoma progression.[4–6] The appropriate detection of these risk factors is important because it can give us the possibility to reduce, at least partially, the likelihood of glaucoma progression through modifying lifestyle habits.[7]

Cigarette smoking is a global public health concern and a well-known risk factor for atherosclerosis and atherosclerotic cardiovascular disease (ASCVD) events.[8] Toxic compounds in tobacco smoke have been found to negatively impact many ocular tissues, mostly through ischemic and oxidative mechanisms.[9] Cataract[10], age-related macular degeneration[11,12], and glaucoma[13] have been more frequently found in cigarette smokers. Previous studies reported controversial results about the association between smoking and incidence of glaucoma.[6,7,14–22] Although some found a link between smoking and glaucoma,[6,7,18,19,21] other studies did not.[14–17,19,20,22] Recent studies suggested that heavy

smoking can increase the risk of POAG and VF progression.[23,24]The pathophysiology of POAG and the effect of smoking have several mechanisms in common, including vascular damage through compromised blood flow and decreasing the outflow of the aqueous humor through trabecular meshwork cells (TMC) and retinal ganglion cells (RGC) damage by high oxidative stress.[13,25,26] Tobacco smoke may negatively affect the blood flow perfusion in the optic nerve head.[27] Moreover, the high oxidative stress with the production of free radicals has been proven to damage TMC and RGC. Additionally, smoking can induce vasoconstriction of the episcleral veins and reduce the aqueous outflow.[28,29] Moderate smoking has also been found to be associated with both diffuse and localized reductions in retinal sensitivity measured by perimetry.[9] Therefore, there is biological plausibility that tobacco smoking may contribute to VF damage in glaucoma eyes.

Smoking cessation has been found to have numerous health benefits and reduces the risk of cardiovascular events, cancer development, and mortality, resulting in significant healthcare cost savings.[30,31] Retinal veins have been observed to return to normal size after more than 10 years of smoking cessation, suggesting that the impact of smoking on the retinal circulation may be reversible.[32] In addition, it was suggested that the risk of age-related macular degeneration (AMD) reduces to a baseline 20 years after smoking cessation.[33] The number of former smokers is growing as US smoking prevalence declines.[34] Therefore, lack of understanding about the long-term effects of smoking cessation may influence glaucoma progression risk assessment among former smokers. However, whether smoking cessation has effects on VF progression in glaucoma eyes and, if so, how long it takes for stopping smoking to reduce the risk has not been well-studied. Such information would be helpful for the management of glaucoma patients, who could be strongly encouraged to change their smoking habits.[35] The purpose of this study was to evaluate the longitudinal effects of smoking cessation on the VF function of glaucomatous patients enrolled from three glaucoma cohorts.

## Methods

This was a retrospective cohort study of POAG patients enrolled in the Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES)[36,37] who underwent standard automated perimetry using the Swedish Interactive Thresholding Algorithm (SITA) Standard 24–2 strategy. All participants provided written informed consent, the Institutional Review Board at the University of California San Diego approved all protocols, and all methods were in compliance with the Declaration of Helsinki.

All participants had an annual comprehensive ophthalmologic evaluation, including best-corrected visual acuity, slit-lamp biomicroscopy, dilated fundus examination, and stereoscopic optic disc photography in both eyes. Semi-annual evaluations included Goldmann applanation tonometry measurement and Standard Automated Perimetry testing. Self-reported history of smoking, smoking duration, packs per day), alcohol consumption, and BMI were also collected. The questionnaire about smoking and alcohol consumption is provided in supplementary Table1.

POAG eyes having a minimum follow-up time of 3 years and a minimum of 5 VFs were included in this study. Eyes were classified as glaucomatous if they had repeatable (at least 2 consecutive) abnormal VF test results with evidence of glaucomatous optic neuropathy – defined as excavation, the presence of focal thinning, notching of the neuroretinal rim, or localized or diffuse atrophy of the retinal nerve fiber layer (RNFL) based on the grading of optic disc photographs. An abnormal VF test was defined as a pattern standard deviation outside of the 95% normal confidence limits or a Glaucoma Hemifield Test result outside normal limits. Glaucoma disease severity was classified as early (24–2 VF mean deviation (MD) >−6 dB), or moderate (−12 dB≤ 24–2 VF MD<−6 dB).[38] All VF tests were performed on the Humphrey Field Analyzer (Carl Zeiss Meditec, Inc., Dublin, CA), with the results being considered unreliable and excluded from the analyses if they had >33% fixation losses or false-negative errors or >15% false-positive errors. In order to avoid the risk of truncation (floor effect), we also removed eyes with VF baseline MD less than −12 dB.[39]

Inclusion criteria included (1) older than 18 years of age, (2) open angles on gonioscopy, and (3) best-corrected visual acuity of 20/40 or better at study entry. Exclusion criteria included (1) history of trauma or intraocular surgery (except for uncomplicated cataract surgery or glaucoma surgery), (2) coexisting retinal disease, uveitis, or non-glaucomatous optic neuropathy, (3) other systemic or ocular diseases known to affect VF such as pituitary lesions or demyelinating diseases, (4) significant cognitive impairment, Parkinson's disease, Alzheimer's disease, dementia, or a history of stroke or (5) axial length of 27 mm or more. We included former smokers at baseline to evaluate the effect of smoking cessation on VF progression.

## Statistical analysis

Patient and eye characteristics data were presented as mean (95% confidence interval (CI)) for continuous variables and count (%) for categorical variables. The smoking intensity was calculated as the pack-year index at the baseline VF. Pack-years index was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. Primary analyses focused on " heavy smokers" (≥20 pack-year smoking history) and never smokers in this study. A priori focus on heavier smokers was based on a prior examination of adverse cardiovascular event risk by smoking status in the Framingham Heart Study.[40,41] Two methods were used for evaluating the progression:

1. **Trend-based analysis:** Linear mixed models estimate the average rate of change in an outcome variable using a linear function of time, and subject- and eye-specific deviations from this average rate are introduced by random slopes.[42,43] Univariable models were first used to evaluate the effect of smoking intensity on the rates of VF MD loss over time, as well as baseline demographics and clinical characteristics. To allow for the interpretation of the effect of smoking intensity, we built multivariable models for smoking intensity that included additional adjustment for mean IOP, race, follow-up time, age baseline MD, as well as alcohol consumption, BMI (which may confound the effect of smoking intensity on VF progression)[4,44] and any other variable in which the P-value was <0.10 in univariable analysis.

2. **Pointwise linear regression (PLR):** Ordinary least squares of the raw threshold sensitivities over time was performed for each of the 52 VF pointwise series. The slope of the regression line, expressed in decibels per year, was defined as the pointwise linear rate of change. The presence of three pointwise series having a significant regression slope ($P < .01$) of −1 dB/y or less was defined as progression.[45]

To perform a Cox proportional hazard regression analysis, VF progression was assessed using a survival analysis method, where an eye was considered to have progressed (i.e., reached an endpoint) if at least 2 consecutive visits during the follow-up had a p-value less than .05 and rates of change below 0. Univariable and multivariable Cox proportional hazard regression analysis with random effect on eyes were used to determine predictive factors for VF progression in former heavy smokers associated with categorical years since quitting.[46] To explore the hazard risk of VF progression over different years of quitting, years since quitting was modeled as a continuous variable (up to 30). Former smokers with more than 30 years since quitting were assigned a value of 31. In Cox proportional hazards regression, the variable of continuous years since quitting was modeled using restricted cubic splines with 4 knots[47] to allow a nonlinear association with the log hazard of VF progression, presented graphically.

Kaplan-Meier survival analysis and the log-rank test were used to compare the cumulative risk ratio of VF progression between former heavy smokers (≥20 pack-years at baseline)[41] with respect to different years of quitting smoking vs. never smokers.

Analyses were also conducted to examine the ORs among former smokers according to the number of years from the time they had last smoked (≥25 years quitting vs. <25 years quitting) to baseline VF using PLR method

In addition to smoking intensity, alcohol consumption status, and BMI were also introduced into the separate multivariable model to explore the effect of these covariates on VF progression. Statistical analyses were performed using Stata version 16.0 (StataCorp, College Station, TX). P values of less than 0.05 were considered statistically significant for all analyses.

## Results

A total of 511 eyes of 354 POAG patients were enrolled in this study. Mean age (95% CI) was 62.3 (61.2,63.4) years. Mean baseline VF MD was −3.3 (−3.6,−3.0) dB. An average of 18.0 (17.4,18.7) VFs was observed over the 12.4 (12.0,12.7) years follow-up period. A total of 149 (42.1%) patients had reported smoking at some time. Among former smokers, the mean smoking pack-year history was 13.2 (10.9,15.5) pack-years. Current alcohol consumption was reported in 168 (59.8%), and mean BMI was 27.2 (26.6,27.9) $kg/m^2$. Demographics and baseline clinical characteristics of the subjects are presented in Table 1.

Supplementary Table 2 summarizes the factors contributing to the rate of VF worsening over time by univariable analysis among former smokers with POAG. Current alcohol

consumption (P=.68) was not associated with VF worsening, while smoking pack-years (β=−0.06 (−0.10,−0.02) μm/year per 10 pack-years higher; P=0.004) was significantly associated with the faster rates of VF worsening over time. Lower BMI (β=0.10 (−0.01,0.18) per 10 kg/m$^2$; P=0.07) tended to be significantly associated with the faster rates of VF worsening over time. Older age, higher baseline IOP, and lower baseline MD were also found to be significantly associated with the faster rates of VF worsening over time (P<0.05 for all).

Table 2 summarizes the multivariable linear mixed models examining the rate of VF worsening over time for smoking pack-years, current alcohol consumption, and BMI separately. After adjustment for confounding factors, current alcohol consumption and BMI were not significantly associated with the rates of VF worsening over time (all P>0.05), while smoking pack-years was significantly associated with the rates of VF worsening over time (β= −0.06 (−0.10,−0.01) dB/year per 10 pack-year higher; P=0.01) after adjustment for alcohol consumption and BMI, and other covariates.

Supplementary Table 3 shows the result of univariable and multivariable analysis for progressors vs. non-progressor eyes according to PLR criteria among former heavy smokers (≥20 pack-years), former mild/moderate smokers (0–20 pack-years), and never smokers. There was no difference in terms of VF progression between former mild/moderate smokers vs. never smokers (P=0.37) and therefore subsequent analysis to assess the effect of smoking cessation on VF progression was limited to former heavy smokers vs. never smokers. Figure 1 displays the relative hazard risk associated with VF progression across the smoking quitting time in years. In cox proportional hazard regression analysis, former heavy smoking quit less than 25 years prior to the baseline VF was significantly associated with VF progression (adjusted HR=2.59(1.45,4.63); P= 0.001) compared to never smokers, while former heavy smokers who had quit more than 25 years prior to the baseline VF were not associated with VF progression (adjusted HR=0.82 (0.32,2.10); P=0.67) as compared to never smokers (Table 3). Likewise, the Kaplan–Meier curve also showed that the former heavy smokers with less than 25 years of smoking cessation had significantly shorter time to VF progression than those with more than 25 years of smoking cessation (P= <0.001, log-rank test)(Figure 2). Similar results were found using the PLR method. Supplementary Table 4 shows the result of univariable and multivariable analysis for progressing eyes vs. non-progressing eyes according to PLR criteria among former heavy smokers (with respect to different duration of quitting) vs. never smokers. Multivariable analysis showed that smoking more than 20 pack-years and quitting within 25 years (OR= 2.49 (1.01,6.08) per 10 pack-year higher; P=0.046) was associated with a statistically significant increase in the odds of VF progression after adjustment for alcohol consumption and BMI. Lower BMI was associated with higher odds of VF progression (OR=0.95 (0.90,0.99) per 10 kg/m$^2$ higher; P=0.04). Moreover, 27.3 % of eyes of patients that quit less than 25 years were of African descent. While 5% of eyes in the smoking group that quit more than 25 years were of African descent.

## Discussion

The current study demonstrated that among individuals with ≥20 pack-year smoking history, 25 years of smoking cessation mitigated VF progression risk to be comparable to those who had never smoked. This reaffirms the benefit of smoking cessation demonstrated for other types of eye disease, especially age-related macular degeneration (AMD),[33,48] and also reduces ensuing VF progression risk over decades. As compared with individuals who never smoked, those with ≥20 pack-year history still had higher VF risk progression within 25 years of cessation. To our knowledge, this is the first study to demonstrate that smoking cessation can reduce VF progression of glaucoma patients.

Our current study showed that the risk of VF progression in former heavy smokers with POAG who quit smoking for 25 years or more is comparable to those who never smoked. This suggests 25 years of smoking cessation may be needed to reduce the cumulative effect of long-term smoking on glaucoma progression, especially in patients with 20 pack-years or more of smoking history. Although the exact amount of time after quitting at which former smokers' VF progression ceases to differ significantly from that of those who never smoked is unknown (and may further depend on cumulative exposure), these findings support a long time course of risk reduction, especially in former heavy smokers.

Glaucoma risk calculators have used criteria such as CCT, IOP, age, increased vertical cup/disc ratio, to help inform patients regarding their risk for development of glaucoma.[49–53] Among well-recognized risk factors, IOP is the only modifiable risk factor.[4] However, the current study shows that clinicians may need to differentiate risk between former and never smokers, and this is also dependent on the time since quitting among former smokers. The proportion of former smokers in the United States increases with more current smokers quitting, so does the potential to underestimate glaucoma progression risk using available well-known risk factors, especially among heavier smokers. The present investigation does not support the assumption that former smokers achieve the same glaucoma risk as never smokers within a short period of time. Future studies should investigate the extent to which including comprehensive data on smoking exposure, such as pack-years smoked and years since quitting, would improve the performance of existing glaucoma risk prediction tools and, by extension, glaucoma management outcomes. Given that smoking status documentation has been included as a meaningful use requirement for electronic health records and has been shown to have robust data coverage in patients with eye diseases including glaucoma, this information is often readily available to ophthalmologists.[54–56]

Individuals with more than 20 pack-years of prior smoking history and less than 25 years of smoking cessation at the baseline VF showed approximately 2.6 times higher risk for glaucoma progression as compared to never smokers. This evidence supports the hypothesis that smoking initiation and lifetime smoking behavior may be causally associated with the risk of VF progression, especially among heavy smokers. The effect of smoking cessation in macular degeneration has been described previously.[33] There is a need for 20 years or more of smoking cessation to reduce the risk of AMD to be similar to that of never smokers.[33,57] In contrast to the many current known risk factors for POAG, tobacco smoking is a modifiable risk factor. Therefore, this result has an important implication in smoking

cessation and public health prevention programs. Prior studies have shown that Americans fear blindness more than other health concerns, including loss of life or limb, and thus the prospect of vision loss may be a powerful motivator for smoking cessation.[58]

Controversial results have existed regarding smoking as a risk factor for glaucoma.[6,7,14–22,59,60] In the current study, higher smoking was independently associated with a faster VF progression over time among smokers with POAG. A few studies reported that cigarette smoking might have a protective effect against glaucoma in a lower dose.[6,61] In the United Kingdom Glaucoma Treatment Study, a history of smoking was negatively associated with VF worsening over 2 years.[6] This maybe because high levels of nitric oxide can induce increased optic nerve blood flow through vasodilation, while nitric oxide can also induce hyperperfusion damage and free radicals that induce RGC death.[62] Additionally, investigators in that study only collected information based on the history of smoking for short follow-up. Heavy smoking over a longer time period may eliminate such protective effects.[18,22,63] Nicotine or other harmful substances can diminish the blood velocity in vessels of the optic nerve head and chorioretina.[64] The cumulative effect of tobacco through chronic nicotine toxicity can have a neurotoxic impact on the optic nerve.

Controversies also exist with regard to the effect of different intensities of smoking on various retinal layers.[65–68] Some cross-sectional studies showed the effect of smoking on different retinal layers thinning.[65,67,68] However, other studies did not find any effect for smoking on RNFL thinning.[69–71] The current observation could shed light on the fact that the cumulative effect of smoking may need a longer time to impact retinal thickness in glaucoma patients.[71,72]

Some cross-sectional studies have investigated the cumulative effect of smoking on VF. Akarsu et al.[9] showed that moderate cigarette smoking (10–20 cigarettes per day for at least the past 5 years) is associated with both diffuse and localized reductions in retinal sensitivity using white on white perimetry. Another study showed that POAG patients with greater pack-years of smoking exhibited more peripheral VF than paracentral VF defect.[73] In healthy chronic heavy smokers, retinal sensitivity was found to be decreased, although the central vision was not affected, possibly due to a cumulative effect of chronic smoking onto the retinal and/or optic nerve functions without clinically evident optic neuropathy.[74] Different levels of nicotine absorption or differences in end-organ response to the combination of chemicals in tobacco smoke can be the possibility that contributes to different effects with different levels of smoking use.[71,72]

This study has some limitations. First, the questionnaire only reflected baseline conditions. We did not include diet and exercise as potential confounders because they were not recorded in our questionnaire. Further study is needed to examine lifestyle changes and glaucoma progression over time. Our study did not consider the effect of environmental tobacco smoking (passive smoking) on glaucoma. Information on environmental tobacco smoke exposure and use of other types of tobacco was not available for most participants and was not included. Also, the amount of alcohol consumption on VF worsening was not considered in the analysis since our questionnaire lacks this information. Second, although a correlation between smoking and VF progression exists, a linear model may not represent

the true demonstration of the effect of smoking on ocular tissue. Third, although our sample size was large enough to address the questions of interest and also provided thoroughly captured longitudinal smoking data, it was not large enough to investigate the effect of smoking cessation in shorter duration brackets. Fourth, we removed glaucoma patients with MD less than −12 dB as PLR does not perform well for detection of glaucoma progression in these patients. Caution should be exercised when extrapolating the results to severe stages of glaucoma. Finally, the current study did not show higher risk for VF progression in former mild/moderate smokers than never smoking; thus, the primary findings are applicable to smokers with a cumulative smoking history of at least 20 pack-years.

In conclusion, this study demonstrated that long-term smoking cessation may reduce VF progression among heavy smokers after 25 years. Current research supports that modifiable factors other than IOP may be related to glaucoma progression. Among heavy smokers, relative to those individuals who never smoked, former smokers' risk remained significantly elevated within 25 years after smoking cessation. These data warrant cessation of smoking among patients with glaucoma, the importance of developing efficient screening for smoking in the clinical setting, especially in high-risk patients, and incorporating this information into public health programs.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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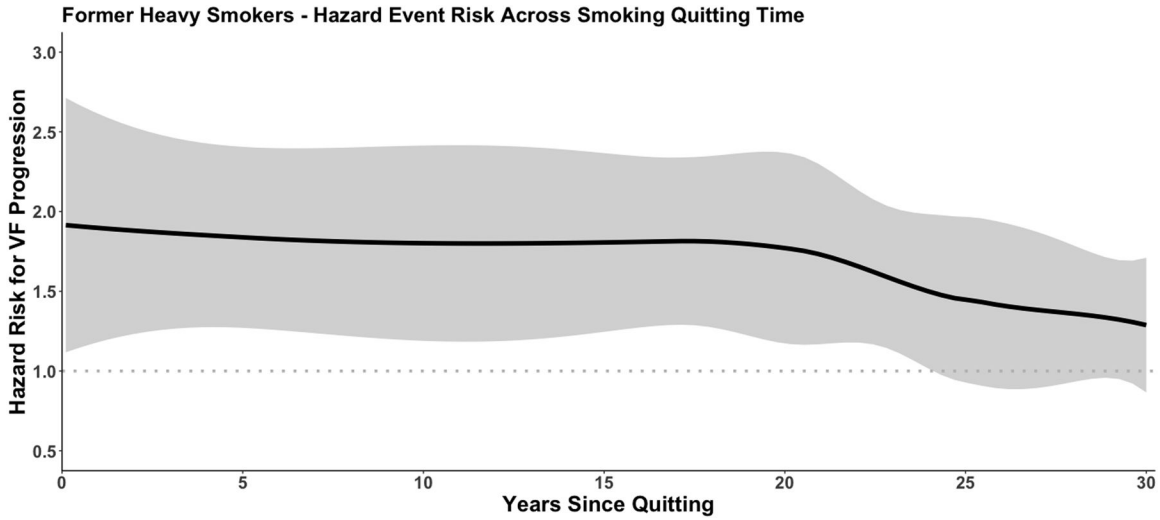


**Figure 1.**

Hazard event risk associated with visual field progression among former smokers vs. never smokers is displayed, containing data from 52 eyes (39 subjects). This plot provides a stable estimate for relative risk of hazard event across a range of 0 to 30 years since quitting smoking. Former smokers are limited to those with at least 20 cumulative pack-years and are adjusted for age, alcohol consumption, body mass index, and mean intraocular pressure (IOP).

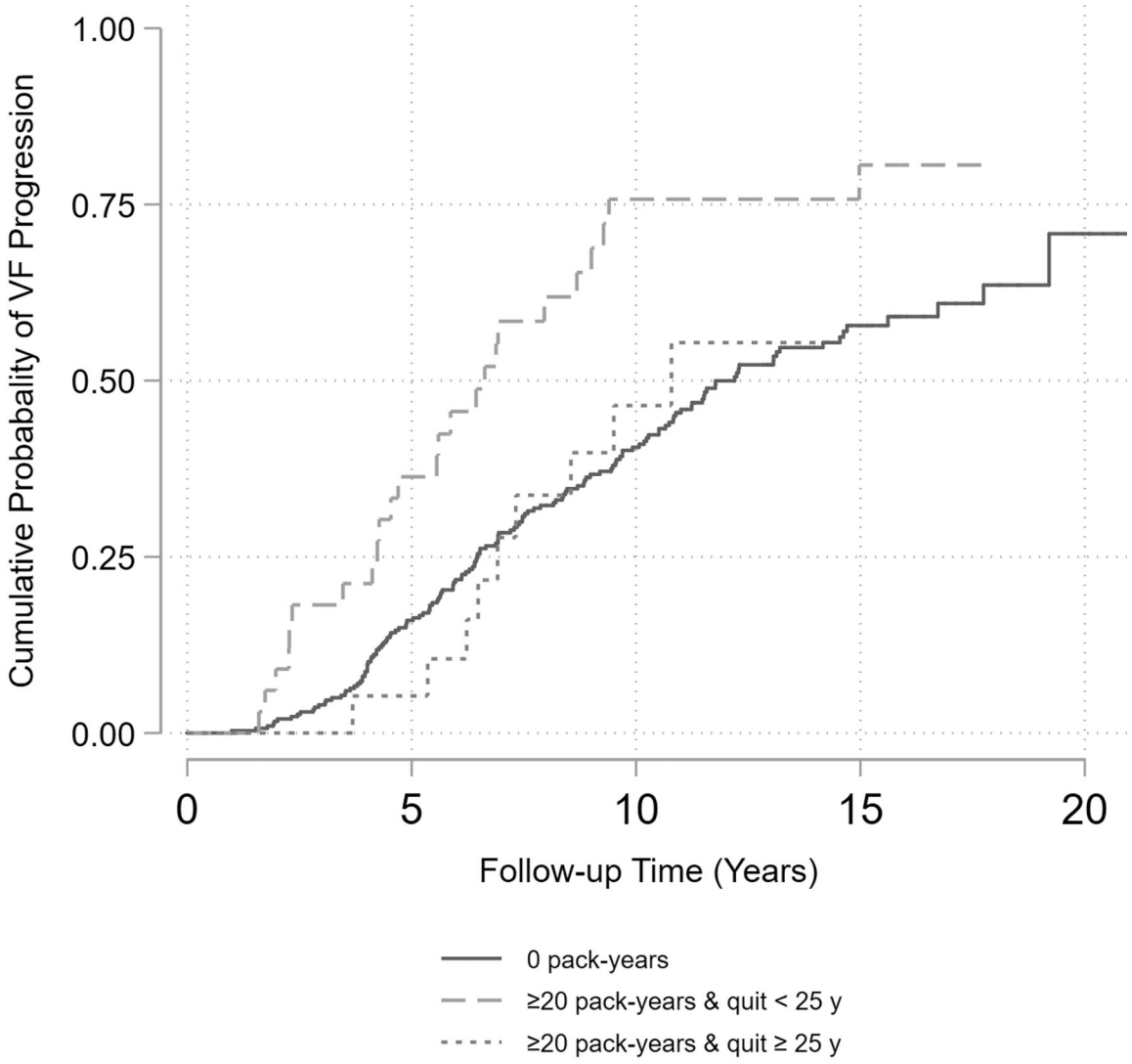


**Figure 2.**

Kaplan-Meier analysis of the probability to detect visual field (VF) progression in glaucoma eyes. Log-rank tests comparing heavy smokers (≥20 pack-years) who quit smoking within 25 years vs. heavy smokers who quit more than 25 years showed a statistically significant difference. (P= <0.001, log-rank test).

**Table 1.**

Demographics and Baseline Characteristics of included eyes.

| Characteristic | n=511 eyes of 354 patients | n=211 eyes of 149 former smokers | n=300 eyes of 205 never smokers |
|---|---|---|---|
| Baseline age (years) | 62.3 (61.2, 63.4) | 64.8 (63.4,66.3) | 60.5(58.9,62.1) |
| Gender (Female/Male), n (%) | 188(53.1%)/166(46.9%) | 75(50.3%)/74(49.7%) | 113(55.1%)/92(44.9%) |
| Race, n (%) (African American/Non-African American) | 124(35.0%)/230(65%) | 37(24.8%)/112(75.2%) | 87(42.4%)/118(57.6%) |
| Ever reported smoking, n (%) | 149 (42.1%) | - | - |
| Smoking pack-years at baseline VF | 5.6(4.4,6.7) | 13.2 (10.9, 15.5) | - |
| Smoking pack-years at baseline VF, n (%) | | | |
| 0 pack-years | 205 (57.9%) | | 205 (57.9%) |
| 0–20 pack-years | 110 (31.1%) | 110 (73.8%) | |
| ≥20 pack-years | 39 (11.0%) | 39 (26.2%) | |
| Current alcohol consumption, n (%) | 168 (59.8%) | 84 (68.9%) | 84 (52.8%) |
| BMI ($kg/m^2$) | 27.2 (26.6, 27.9) | 26.8 (25.9,27.8) | 27.5 (26.7,28.4) |
| Self-reported hypertension, n (%) | 229 (64.7%) | 105 (70.5%) | 124 (60.5%) |
| Self-reported diabetes, n (%) | 80 (22.6%) | 37 (24.8%) | 43 (21.0%) |
| Axial length (mm) | 24.0 (23.9, 24.1) | 24.1 (23.9,24.3) | 24 (23.8,24.1) |
| CCT (μm) | 542.8 (539.3, 546.3) | 547.3 (541.5, 553.1) | 539.6 (535.3,544.0) |
| Baseline IOP (mmHg) | 18.3 (17.7, 18.9) | 19.3 (18.4,20.2) | 17.6 (16.9,18.3) |
| Mean IOP during follow-up (mmHg) | 15.2 (14.9, 15.6) | 15.3 (14.8,15.8) | 15.2 (14.8,15.6) |
| Disease Severity by baseline 24–2 VF MD | | | |
| Early glaucoma, Eye No. (%) | 414 (81.0%) | 169 (80.1%) | 245 (81.7%) |
| Moderate glaucoma, Eye No. (%) | 97 (19.0) | 42 (19.9%) | 55 (18.3%) |
| Baseline VF MD (dB) | −3.3 (−3.6, −3.0) | −3.2 (−3.7,−2.7) | −3.4 (−3.7,−3.0) |
| VF follow-up visits (n) | 18.0 (17.4, 18.7) | 18.7 (17.8,19.5) | 17.2 (16.1,18.2) |
| Follow-up (years) | 12.4 (12.0, 12.7) | 12.2 (11.6,12.8) | 12.4 (12.0,12.7) |
| Time between Smoking cessation and baseline VF (years) | - | 28.8 (27.2,30.4) | - |
| Time between Smoking questionnaire and baseline VF (years) | 10.1 (9.7,10.5) | 10.3 (9.6,10.9) | 10.0 (9.4,10.5) |

BMI = Body Mass Index; CCT = Central Corneal Thickness; IOP = Intraocular Pressure; MD = Mean Deviation; OCT = Optical Coherence Tomography; VF = Visual Field; n = number. Values are shown in mean (95% confidence interval), unless otherwise indicated.

**Table 2.**

Multivariable Linear Mixed Models Assessing the Rate of Visual Field Loss Over Time in Smokers

| Variables | Multivariable Model 1 (Smoking pack-years) | | Multivariable Model 2 (BMI) | | Multivariable Model 3 (Alcohol) | | Multivariable Model 4 (Smoking pack-years adjusted for Alcohol consumption and BMI) | |
|---|---|---|---|---|---|---|---|---|
| | Coefficient, 95% CI | P value | Coefficient, 95% CI | P value | | | Coefficient, 95% CI | P value |
| Smoking pack-years, per 10 pack-years higher | −0.04 (−0.08,−0.00) | 0.06 | - | - | - | - | −0.06 (−0.10,−0.01) | **0.01** |
| Current alcohol consumption, yes | - | - | - | - | −0.02 (−0.15,0.11) | 0.76 | −0.01 (−0.14,0.12) | 0.92 |
| BMI, per 10 kg/m$^2$ higher | - | - | 0.03 (−0.07,0.12) | 0.56 | | - | 0.03 (−0.08,0.15) | 0.54 |
| Baseline age (year) per 10 years | −0.01 (−0.02,−0.01) | **<0.001** | −0.01 (−0.02,−0.01) | **<0.001** | −0.02 (−0.02,−0.01) | **<0.001** | −0.01 (−0.02,−0.01) | **0.001** |
| Ethnicity: African Descent | 0.05 (−0.07,0.16) | 0.41 | 0.05 (−0.07,0.17) | 0.42 | 0.13 (−0.40,0.66) | 0.62 | 0.07 (−0.06,0.20) | 0.28 |
| CCT, per 100 μm thinner | | | | | | | | |
| Mean IOP during follow-up (mmHg) per 1 mmHg higher | −0.02 (−0.04,−0.01) | **0.002** | −0.02 (−0.03,−0.00) | **0.01** | −0.03 (−0.04,−0.01) | **0.002** | − 0.03 (−0.04,−0.01) | **0.001** |
| Baseline 24–2 VF MD (dB) per 1 dB worse | 0.02 (0.01,0.04) | **0.01** | 0.02 (0.00,0.03) | **0.01** | 0.02 (0.01,0.04) | **0.01** | 0.02 (0.00,0.03) | **0.03** |

BMI = Body Mass Index; IOP = Intraocular Pressure; MD = Mean Deviation; VF = Visual Field. Values are shown in mean (95% confidence interval), unless otherwise indicated. Bold text indicates a statistically significant difference with a p-value less than 0.05.

Model 1 included smoking intensity while adjusting for age, race, baseline MD, and mean IOP.

Model 2 included BMI while adjusting for age, race, baseline MD, and mean IOP.

Model 3 included BMI while adjusting for age, race, baseline MD, and mean IOP.

Model 4 included smoking intensity while adjusting for age, race, baseline MD, mean IOP, alcohol consumption, and BMI.

**Table 3.**

Univariate and Multivariable Cox Proportional Hazard Model Assessing VF Progression in Heavy (≥20 pack-years) Smokers with POAG.

| Variables | Univariable Model | | Multivariable Model | |
|---|---|---|---|---|
| | HR (95% CI) | P Value | HR (95% CI) | P value |
| Smoking intensity (reference: never smokers) | | | | |
| Quit ≥ 25 years | 1.03 (0.53,2.02) | 0.93 | 0.82 (0.32,2.10) | 0.67 |
| Quit <25 years | 2.20 (1.44,3.37) | **<0.001** | 2.59 (1.45,4.63) | **0.001** |
| Current alcohol consumption, yes | 1.26 (0.88,1.79) | 0.21 | 1.13 (0.79,1.60) | 0.51 |
| BMI, per 10 kg/m$^2$ higher | 0.97 (0.95,1.00) | **0.04** | 0.97 (0.94,1.00) | 0.09 |
| Baseline age (year) per 10 years | 1.18 (1.00,1.40) | **0.05** | 1.05 (0.87,1.28) | 0.60 |
| Gender: female | 1.04 (0.75,1.43) | 0.82 | | |
| Ethnicity: African Descent | 0.86 (0.62,1.18) | 0.35 | | |
| Self-reported hypertension | 0.95 (0.65,1.29) | 0.77 | | |
| Self-reported Diabetes | 0.93 (0.65,1.33) | 0.69 | | |
| Axial length, per 1mm longer | 1.01 (0.87,1.18) | 0.86 | | |
| CCT, per 100 μm thinner | 0.83 (0.52 ,1.33) | 0.44 | | |
| Baseline IOP during follow-up (mmHg) per 1 mmHg higher | 1.02 (1.00,1.05) | 0.08 | | |
| Mean IOP during follow-up (mmHg) per 1 mmHg higher | 1.02 (0.98, 1.07) | 0.38 | 1.05 (1.00,1.11) | **0.04** |
| Baseline 24–2 VF MD (dB) per 1 dB worse | 1.04 (0.98,1.11) | 0.16 | | |

BMI = Body Mass Index; IOP = Intraocular Pressure; MD = Mean Deviation; VF = Visual Field, POAG=Primary Open Angle Glaucoma, HR=Hazard Ratio. Multivariable model was adjusted for age, mean IOP during follow-up, current alcohol consumption, and BMI. Values are shown in mean (95% confidence interval), unless otherwise indicated. Bold text indicates a statistically significant difference with a p-value less than 0.05.