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# BMJ Open Associations of smoking and alcohol consumption with the development of open angle glaucoma: a retrospective cohort study

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## ABSTRACT

**Objectives** To investigate the associations of alcohol consumption and smoking with the development of perimetric glaucoma in patients with suspected glaucoma.

**Design** A retrospective cohort study of patients suspected to have glaucoma enrolled in the Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES).

**Setting** Three tertiary glaucoma centres in the USA.

**Participants** 825 eyes of 610 patients with glaucoma suspect eyes with normal visual fields (VF) at baseline were followed over an average of 9 years from the DIGS and ADAGES studies.

**Outcome measures** Development of glaucoma was defined as occurrence of three consecutive abnormal VF tests during follow-up. Univariable and multivariable Cox regression models were used to investigate lifestyle-related factors associated with development of VF loss over time.

**Results** VF tests were abnormal three times in a row in 235 (28.5%) eyes. Alcohol consumption was associated with a higher risk of developing glaucoma (HR 1.57, 95% CI 1.03 to 2.38,  $p=0.037$ ). In men, the risk of developing glaucoma in alcohol drinkers (HR 1.92, 95% CI 1.00 to 3.68,  $p=0.048$ ) was greater than non-alcohol drinkers. In individuals of African descent, the risk of developing glaucoma in alcohol drinkers (HR 1.79, 95% CI 1.02 to 3.15,  $p=0.043$ ) was greater than non-alcohol drinkers. Age was a modifier of the relationship between smoking and glaucomatous VF defects ( $p=0.048$ ). The risk of developing glaucoma in smokers (HR 1.73, 95% CI 1.10 to 2.72,  $p=0.019$ ) was greater than never smokers after adjustment for confounding factors in older patients (age >61 years).

**Conclusion** Alcohol consumption was associated with an increased risk of developing glaucoma, particularly in men and individuals of African descent. The risk of developing glaucoma among smokers suspected of having glaucoma was influenced by age, with older individuals having a higher risk than younger people.

**Trial registration number** NCT00221897 and NCT00221923.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This was a multicentre study and included a large number of patients with suspected glaucoma who were followed up over a long period.
- ⇒ A limitation was that information on environmental tobacco smoke exposure and use of other types of tobacco was not available for most participants.
- ⇒ Another limitation was that the amount of alcohol consumption was not considered in the analysis because our questionnaire lacked this information.

## INTRODUCTION

Glaucoma is a progressive optic neuropathy characterised by retinal ganglion cell degeneration and associated visual field (VF) damage.<sup>1</sup> Given the chronic, progressive, and irreversible nature of glaucoma, understanding risk factors that influence glaucoma development is important.<sup>2</sup> Elevated intraocular pressure (IOP) is currently the main risk factor for glaucoma development and progression.<sup>3</sup> However, not every patient with ocular hypertension will develop glaucoma, and glaucoma may also develop in those with an apparently normal IOP.<sup>2</sup> These observations suggest that primary open angle glaucoma (POAG) represents a complex interplay of genetic, environmental, anatomic, and physiologic factors.<sup>4</sup>

Identifying patients' risk factors, especially modifiable ones, for glaucoma development allows clinicians to identify high-risk individuals who may be targeted for closer monitoring or more aggressive treatment.<sup>3 5 6</sup> Other modifiable risk factors besides IOP that may be associated with glaucoma include nutritional intake, body mass index (BMI), and smoking.<sup>3</sup> Addressing these risk factors may provide the possibility to reduce, at least

partially, the likelihood of glaucoma development by modifying lifestyle habits.<sup>7,8</sup>

Glaucoma pathophysiology and ocular toxicity from smoking have several mechanisms in common. These mechanisms include vascular damage by impaired blood flow,<sup>9</sup> decreasing the outflow of the aqueous humour by damaging trabecular meshwork cells and vasoconstriction of the episcleral veins,<sup>10,11</sup> as well as damaging retinal ganglion cells by high oxidative stress.<sup>10–12</sup> Accordingly, there is a biological plausibility that smoking has a role in the development of POAG.

Several studies have published equivocal results regarding the association between smoking and the incidence of glaucoma.<sup>3</sup> Prior longitudinal studies have shown a positive relationship between history of smoking and VF progression.<sup>13</sup> Moreover, it was reported recently that the level of smoking, especially heavy smoking, was associated with a higher risk of VF progression in glaucoma patients.<sup>7</sup>

The impact of alcohol on ocular tissues, particularly long-term effects, is less clear.<sup>14</sup> While elevated IOP has been found to be a long-term effect of alcohol consumption,<sup>14,15</sup> decreased IOP has conversely been found to be a short-term effect. However, the precise physiologic mechanism for IOP reduction remains unclear.<sup>14</sup> The acute effects of alcohol result in a dose-dependent and transient IOP reduction, as well as an increase in blood flow to the optic nerve head.<sup>14,16</sup> However, the chronic systemic effects of alcohol consumption have been associated with neurodegenerative, cardiovascular, and endocrine disorders, as well as systemic biochemical and physiologic derangements.<sup>14</sup>

The relationship between alcohol use and IOP is controversial,<sup>14,15</sup> and the association between alcohol and glaucoma in cross-sectional<sup>14,17</sup> and longitudinal studies is discrepant.<sup>14,18</sup> A recent meta-analysis of published studies reported a positive association between alcohol consumption and POAG incidence and prevalence.<sup>14</sup>

As the impact of modifiable lifestyle factors (ie, alcohol consumption or smoking) on glaucoma development remains unclear, we evaluated these potential associations in glaucoma suspect eyes using data from three glaucoma registries that consist of glaucoma suspect eyes, including a large proportion of patients of African American descent.

## METHODS

### Study design and procedures

This was a retrospective cohort study of patients suspected to have glaucoma enrolled in the Diagnostic Innovations in Glaucoma Study (DIGS) (NCT00221897) and the African Descent and Glaucoma Evaluation Study (ADAGES) (NCT00221923).<sup>19,20</sup> All DIGS and ADAGES participants were recruited as part of a multicentre collaboration that included three tertiary glaucoma centres in the USA: the UCSD Hamilton Glaucoma Centre (San Diego, CA), Columbia University Medical Centre

Edward S. Harkness Eye Institute (New York, NY), and the University of Alabama at Birmingham Department of Ophthalmology (Birmingham, AL). Patients underwent standard automated perimetry (SAP) using the Swedish Interactive Thresholding Algorithm (SITA) Standard 24–2 strategy. All participants provided written informed consent. Patients were consented at the beginning of the study. The Institutional Review Board (IRB 140276) at the University of California San Diego approved all protocols, and all methods complied with the Declaration of Helsinki. Patients who participated in DIGS and ADAGES were compensated (US\$50 (£40, €46)) for each of their twice-yearly visits. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

All participants underwent 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 SAP testing. Self-reported history of smoking and alcohol consumption were recorded in a questionnaire (online supplemental eTable 1). BMI was also recorded for the participants. Patients were followed up from 12 July 1998 to 3 March 2021. Data analysis for the current study was undertaken in February 2022, and all participants from the study who met the inclusion criteria described below were included.

Patients who were suspected to have glaucoma (history of IOP >21 mm Hg and/or suspicious appearance of the optic nerve, but normal and reliable VF results at baseline) with open angles on gonioscopy with a minimum of three VFs and a minimum follow-up time of 1 year were included in this study. Participants were followed every 6 months. 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. SAP tests were performed using the SITA Standard 24–2 strategy on the Humphrey Field Analyzer (Carl Zeiss Meditec, Inc, Dublin, CA, USA). VFs with >33% fixation losses, or >15% false-positive errors, were excluded.

During follow-up, eyes were classified as having developed glaucoma if they demonstrated repeatable (at least three consecutive) abnormal VF test results.<sup>21</sup> For eyes that developed glaucoma, follow-up time was defined as the time between the baseline VF visit and the date of the first of three consecutive abnormal VF results. An abnormal VF was defined as a pattern standard deviation

with  $p < 0.05$  or a Glaucoma Hemifield Test result outside normal limits. Otherwise, the VF was defined as normal. Each patient was treated at the discretion of the attending ophthalmologist.

### Statistical analysis

Patient and eye characteristics data were presented as mean (95% CI) for continuous variables and count (%) for categorical variables. Univariable and multivariable Cox proportional hazard regression analysis with random effects on eyes were used to determine predictive lifestyle factors (ie, smoking, alcohol consumption, and BMI) on glaucoma development. An inter-eye correlation was also considered. In the Cox proportional hazards model, a robust cluster estimation adjustment was added, in order to adjust model estimates for within subject inter-eye correlation. The chosen robust clustering method sums residuals within patient clusters before entering them into subsequent calculations of the variance-covariance matrix. This method was developed by Lin and Wei.<sup>22</sup> To perform a Cox proportional hazard regression analysis, glaucoma development was assessed among two groups: eyes developing repeatable VF defects (VFD) (VFD group) and eyes that did not develop VFD (non-VFD group). In multivariable analysis, in addition to smoking history, alcohol consumption, BMI, and confounding factors for glaucoma development (ie, baseline mean deviation, self-reported race, self-reported sex, mean IOP, and age), and all variables with  $p$  values  $< 0.2$ , were also introduced into the model to explore the confounding relationship of these covariates on glaucoma development. Subsequently, additional models were also fitted to explore the interaction of confounders on the effect of alcohol or smoking on glaucoma development while adjusting for potential confounding factors. To evaluate the interactions between age and history of smoking, as well as between sex or race and the effect of alcohol on glaucoma development, we included the corresponding interaction terms in the Cox proportional hazards regression models, after adjusting for other covariates. We examined the significance of the interaction terms by checking their  $p$  values and confidence intervals in the multivariable analysis. For both interactions, statistically significant  $p$  values ( $p < 0.05$ ) indicated that the interaction terms had a significant effect on the outcome of interest. Afterwards, we evaluated the effect of smoking in different categories of ageing, as well as alcohol in different categories of race and gender using multivariable Cox proportional hazards regression.

Kaplan-Meier survival analysis was used to show the association of smoking with glaucoma development across different levels of age (based on median of age in study population  $\leq 61$  years vs  $> 61$  years). Moreover, Kaplan-Meier survival analysis was used to show the effect of sex on the risk of alcohol consumption with respect to glaucoma development, as prior studies have suggested that race and sex could possibly confound the effect of alcohol consumption on glaucoma.<sup>23 24</sup>

Statistical analyses were performed using Stata version 16.0 (StataCorp, College Station, TX, USA)

### RESULTS

This study included 825 eyes from 610 patients with suspected glaucoma, as determined on the baseline visit, and these patients were subsequently followed for an average of 9.0 (8.7–9.3) years; 235 eyes (28.5%) of 196 patients developed repeatable VF defects during follow-up. Table 1 presents baseline demographic and clinical factors of the study sample. Mean (SD) age was 63.3 (10.7) years at baseline in patients who developed glaucoma and 59.8 (10.9) years at baseline in those who did not ( $p < 0.001$ ). Eyes that developed glaucoma had lower 24–2 VF mean deviation (MD) values compared with those who did not ( $-1.0$  ( $-1.2$  to  $-0.8$ ) dB vs  $-0.4$  ( $-0.5$  to  $-0.3$ ) dB,  $p < 0.001$ ). There was no difference in sex ( $p = 0.373$ ) and race ( $p = 0.556$ ) between the two groups. Patients who developed glaucoma had a higher history of smoking ( $p = 0.052$ ), higher alcohol consumption ( $p = 0.018$ ), lower mean IOP ( $p = 0.034$ ), higher self-reported hypertension ( $p = 0.014$ ), and higher self-reported diabetes ( $p = 0.005$ ) at baseline than patients who did not develop glaucoma. One hundred and ten (18%) patients were both chronic smokers and alcohol consumers.

Table 2 presents hazard ratios (HRs) with 95% CI for risk factors associated with the development of glaucoma. Positive smoking history was associated with an increase of 43% on the risk of developing glaucoma during follow-up (HR 1.43, 95% CI 1.08 to 1.89,  $p = 0.012$ ). However, this association did not persist in a multivariable model adjusting for confounding factors (HR 1.15, 95% CI 0.80 to 1.65,  $p = 0.439$ ). In contrast, current alcohol consumption (HR 1.57, 95% CI 1.03 to 2.38,  $p = 0.037$ ) was associated with glaucoma development in the multivariable model.

### Factors affecting association (interactions) of smoking/ alcohol consumption and glaucoma development

We found an interaction between age and history of smoking and development of glaucomatous VF defects in which the impact of smoking was greater on glaucoma development for older patients than in younger patients (HR 1.45 per positive history of smoking and 10 years older at baseline, 95% CI 1.01 to 2.10,  $p = 0.048$ ), even after adjusting for other variables. Figure 1 shows cumulative probabilities of developing glaucoma at different levels of age ( $> 61$  years vs  $\leq 61$  years) between smokers and never smokers. The risk of developing glaucoma in smokers (HR 1.73, 95% CI 1.10 to 2.72,  $p = 0.019$ ) was greater than never smokers after adjustment for confounding factors in older patients ( $> 61$  years) (online supplemental eTable 2).

There was an interaction between sex and the effect of alcohol on glaucoma development after adjustment for confounding factors ( $p = 0.034$ ), with men having 2.33 times higher risk than women for developing glaucoma.

**Table 1** Demographics and baseline characteristics of included eyes

Characteristic	Developed glaucoma (n=235 eyes, 196 patients)	Did not develop glaucoma (n=590 eyes, 414 patients)	P value
By participants			
Baseline age (years), mean (SD)	63.3 (10.7)	59.8 (10.9)	<0.001
Sex (male), n (%)	87 (44.4%)	168 (40.6%)	0.373
Race, n (%)			0.556
African American	64 (32.7)	124 (30.0)	
Asian	4 (2.0)	14 (3.4)	
White	127 (64.8)	268 (64.7)	
Others	1 (0.5)	8 (1.9)	
Ever reported smoking, n (%)	91 (46.4%)	158 (38.2%)	0.052
Active smoker, n (%)	12 (13.2%)	37 (23.4%)	0.051
Current alcohol consumption, n (%)	95 (48.5%)	129 (31.2%)	<b>0.018</b>
BMI (kg/m <sup>2</sup> )	27.2 (26.4 to 28.0)	27.5 (26.9 to 28.1)	0.552
Self-reported hypertension, n (%)	134 (68.4%)	240 (58.0%)	<b>0.014</b>
Self-reported diabetes, n (%)	46 (23.5%)	59 (14.3%)	<b>0.005</b>
By eyes			
Axial length (mm)	24.0 (23.9 to 24.1)	24.0 (23.9 to 24.1)	0.778
CCT (µm)	551.3 (546.4 to 556.3)	553.8 (550.4 to 557.2)	0.465
Baseline IOP (mm Hg)	19.1 (18.3 to 19.8)	20.1 (19.6 to 20.5)	<b>0.044</b>
Mean IOP during follow-up (mm Hg)	17.4 (16.7 to 18.0)	18.2 (17.9 to 18.6)	<b>0.034</b>
Baseline 24–2 VF MD (Db)	−1.0 (−1.2 to −0.8)	−0.4 (−0.5 to −0.3)	<0.001
VF follow-up visits (n)	10.9 (10.1 to 11.6)	12.7 (12.1 to 13.3)	<0.001
Follow-up (years)	7.5 (6.9 to 8.0)	9.6 (9.2 to 10.0)	<0.001
Time between smoking questionnaire and baseline VF (years)	10.1 (9.5 to 10.6)	7.7 (7.3 to 8.1)	<0.001
Values are shown in mean (95% CI), unless otherwise indicated. BMI, body mass index; CCT, central corneal thickness; IOP, intraocular pressure; MD, mean deviation; n, number; OCT, optical coherence tomography; VF, visual field.			

The risk of developing glaucoma in alcohol drinkers (HR 1.92, 95% CI 1.00 to 3.68,  $p=0.048$ ) was greater than non-alcohol drinkers after adjustment for confounding factors in men (online supplemental eTable 3). **Figure 2** shows cumulative probabilities of developing glaucoma in alcohol drinkers versus non-alcohol drinkers in men versus women. In the interaction between race and effect of alcohol, patients of African descent (AD) tended to have 2.07 times higher risk of developing glaucoma than non-AD patients, although this did not reach statistical significance ( $p=0.066$ ). The risk of developing glaucoma in alcohol drinkers (HR 1.79, 95% CI 1.02 to 3.15,  $p=0.043$ ) was greater than non-alcohol drinkers after adjustment for confounding factors in AD (online supplemental eTable 3). **Figure 3** shows cumulative probabilities of developing glaucoma in alcohol drinkers versus non-alcohol drinkers in AD versus non-AD.

## DISCUSSION

In the present study, we have shown that alcohol consumption is associated with an increased likelihood of developing glaucoma. The association of alcohol consumption

and glaucoma development was more pronounced in males and individuals of AD. Age was a modifier of the relationship between smoking and glaucomatous VF defects. For older patients, the impact of smoking was greater on glaucoma development than in younger ones. To our knowledge, this is the first longitudinal study that shows the effect of alcohol consumption and smoking on glaucoma development in glaucoma suspect eyes.

An association between smoking and developing glaucoma was found in the univariable model. The risk of developing glaucoma in smokers was greater than never smokers after adjustment for confounding factors in older patients (>61 years). Therefore, the potential risk of smoking on glaucoma development should not be ignored, especially in older individuals. Previous studies suggested that ageing may increase the vulnerability of the optic nerve to IOP-related damage, and older patients may require lower IOP than younger ones to prevent disease progression.<sup>25</sup> Tobacco smoke contains many toxic compounds which harm the ocular tissues, triggering ischaemic or oxidative mechanisms. Other detrimental effects of smoking on the eye have also been

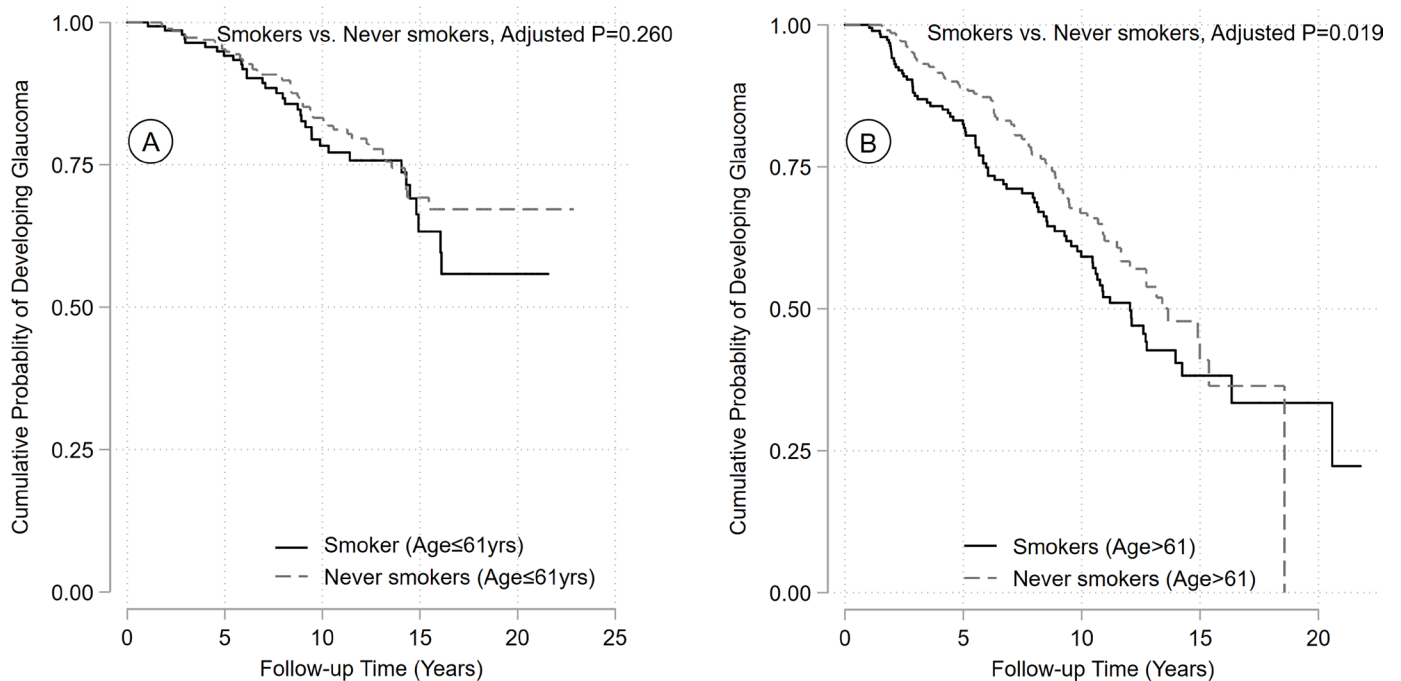
**Table 2** Hazard ratios with 95% CIs for risk factors associated with development of glaucoma

Variables	Univariable model		Multivariable model	
	HR (95% CI)	P value	HR (95% CI)	P value
Smoking history: smoker	1.43 (1.08 to 1.89)	0.012	1.15 (0.80 to 1.65)	0.439
Current alcohol consumption, yes	1.17 (0.80 to 1.71)	0.413	1.57 (1.03 to 2.38)	<b>0.037</b>
BMI, per 10 kg/m <sup>2</sup> higher	0.98 (0.96 to 1.01)	0.192	1.00 (0.97 to 1.03)	0.943
Baseline age (year) per 10 years	1.66 (1.42 to 1.94)	<b>&lt;0.001</b>	1.57 (1.31 to 1.88)	<b>&lt;0.001</b>
Sex: female	0.82 (0.62 to 1.10)	0.170	0.78 (0.55 to 1.12)	0.179
Race: African descent	1.15 (0.84 to 1.55)	0.384	1.47 (0.98 to 2.21)	0.063
Self-reported hypertension	1.21 (0.90 to 1.64)	0.201		
Self-reported diabetes	1.46 (1.05 to 2.02)	<b>0.024</b>	1.12 (0.71 to 1.77)	0.633
Axial length, per 1 mm longer	0.95 (0.85 to 1.07)	0.427		
CCT, per 100 µm thinner	1.00 (0.99 to 1.00)	0.135	1.00 (1.00 to 1.01)	0.633
Baseline IOP during follow-up (mm Hg) per 1 mm Hg higher	0.97 (0.95 to 0.99)	<b>0.018</b>		
Mean IOP during follow-up (mm Hg) per 1 mm Hg higher	0.97 (0.93 to 1.01)	0.196	1.00 (0.95 to 1.05)	0.883
Baseline 24–2 VF MD (dB) per 1 dB worse	0.79 (0.73 to 0.86)	<b>&lt;0.001</b>	0.80 (0.73 to 0.88)	<b>&lt;0.001</b>

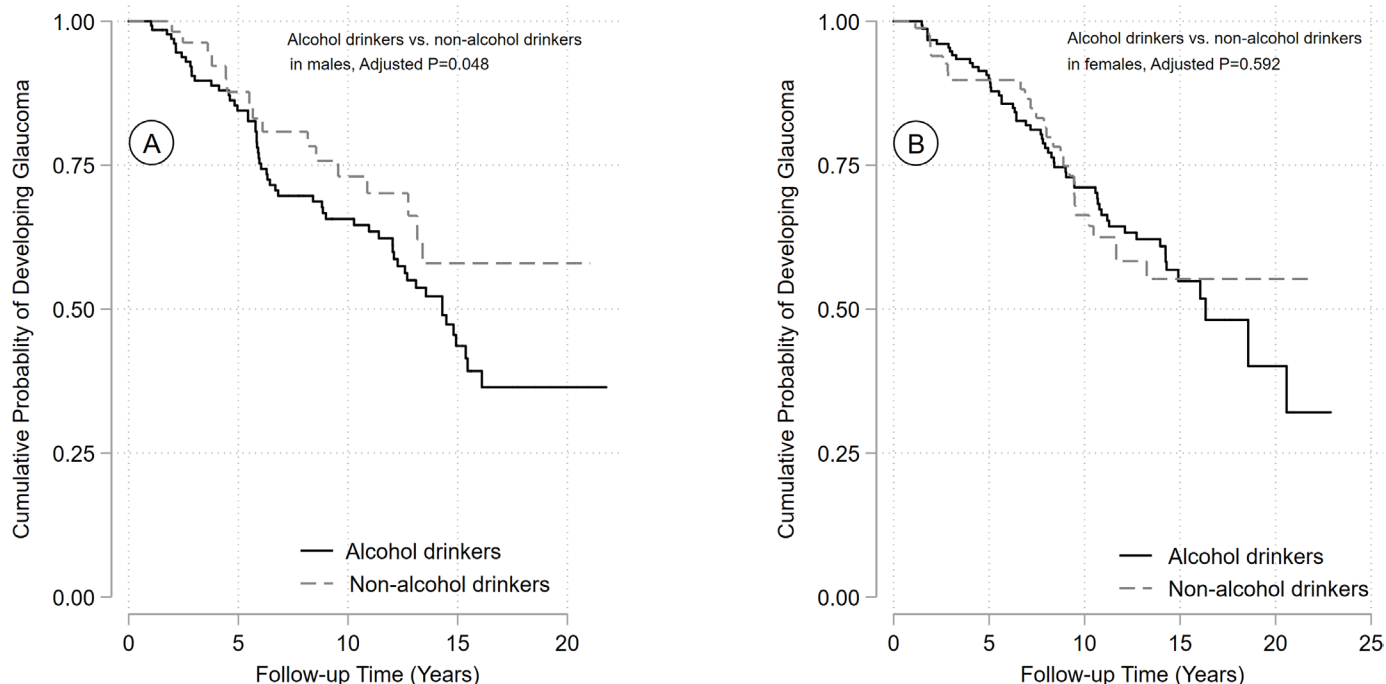
Values are shown in mean (95% CI), unless otherwise indicated. Multivariable models were adjusted for mean IOP, current alcohol consumption, BMI and any variables with a p value <0.05 in univariable models. Bold text indicates a difference with a p value <0.05. BMI, body mass index; CCT, central corneal thickness; IOP, intraocular pressure; MD, mean deviation; POAG, primary open angle glaucoma; VF, visual field.

proposed, including compromised arterial blood flow to the optic nerve head,<sup>9</sup> and inducing vasospasms.<sup>26</sup> Several studies have examined the immediate impact of smoking on optic nerve and macular perfusion using optical coherence tomography angiography among smokers, and have reported conflicting findings.<sup>27–29</sup> Aayhan *et al*<sup>27</sup> did not observe any change in macular vessel density or

foveal avascular zone area 1 hour after smoking. However, they reported that smoking led to decreased blood flow index in the choriocapillary area due to the acute effects of nicotine and other harmful substances in cigarettes on the peripheral vascular structure. In addition, in a recent study, smoking intensity has been shown to be associated with reduced optic nerve vessel density in glaucoma



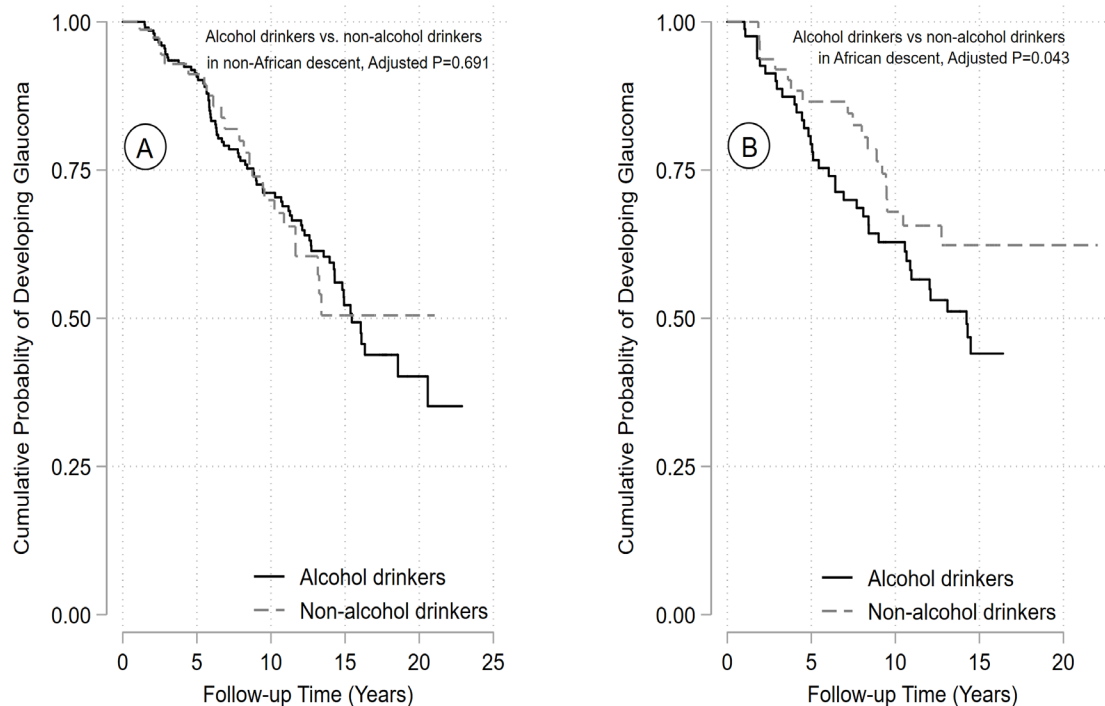
**Figure 1** Cumulative probability of glaucoma development in glaucoma suspect eyes between smokers and never smokers at different levels of age ( $\leq 61$  years in panel A vs  $> 61$  in panel B). In panel A, 34 (23.8%) and 50 (18.5%) of eyes developed glaucoma in smokers versus never smokers, respectively. In panel B, 79 (40.9%) versus 72 (32.8%) of eyes developed glaucoma in smokers versus never smokers, respectively.



**Figure 2** The cumulative probability of glaucoma development in glaucoma suspect eyes between alcohol drinkers and non-alcohol drinkers by sex (men in panel A vs women in panel B). In panel A, 58 (43.3%) versus 16 (27.6%) of eyes developed glaucoma in alcohol drinkers versus non-alcohol drinkers. In panel B, 27 (37.0%) versus 57 (32.1%) of eyes developed glaucoma in alcohol drinkers versus non-alcohol drinkers.

patients.<sup>9</sup> Therefore, the effect of smoking on the vasculature may explain the reason for higher vulnerability of older patients to smoking than younger adults.

Equivocal results have been reported regarding smoking as a risk factor for glaucoma.<sup>13 17</sup> Some studies have found an association between smoking and glaucoma<sup>13 30</sup> while



**Figure 3** The cumulative probability of glaucoma development in glaucoma suspect eyes between alcohol drinkers and non-alcohol drinkers by ethnicity (non-African descent in panel A versus African descent in panel B). In panel A, 77 (37.6%) versus 24 (31.2%) of eyes developed glaucoma in alcohol drinker versus non-alcohol drinkers. In panel B, 38 (45.8%) versus 19 (29.2%) of eyes developed glaucoma in alcohol drinker versus non-alcohol drinkers.

others did not find any.<sup>31</sup> Moreover, cigarette smoking was not found to be associated with severity of primary angle closure glaucoma (PACG).<sup>32</sup> However, the number of cigarettes smoked per day was associated with the severity of PACG and this association was influenced by sex.<sup>32</sup> In the longitudinal United Kingdom Glaucoma Treatment Study, a history of smoking was negatively associated with VF worsening over 2 years.<sup>13</sup> In contrast, in a recent report by Mahmoudinezhad *et al*, higher smoking intensity, especially heavy smoking, was associated with higher risk of glaucoma progression over 12 years of follow-up.<sup>7</sup> It was also suggested that ageing increases the risk of smoking on glaucoma progression. Similarly, in this current study, we found that ageing increases the risk of smoking on perimetric glaucoma development among patients with suspected glaucoma.

Alcohol consumption was associated with a 1.6-fold higher risk of developing glaucoma in the multivariable model. Previous studies had conflicting reports regarding the association of alcohol consumption and POAG.<sup>14</sup> Alcohol use has not been associated with VF deterioration in known glaucoma patients or glaucoma development from patients with suspected glaucoma.<sup>14 33</sup> Also, several observational studies found no association between alcohol drinking and glaucoma prevalence.<sup>14</sup> However, prospective studies showed an increased risk of glaucoma prevalence in alcohol consumers.<sup>14 23 34</sup> Moreover, high levels of alcohol consumption (daily or almost daily alcohol consumption<sup>35</sup>: women  $\geq 10$  g/day; men  $\geq 20$  g/day)<sup>36</sup> have been found to be particularly associated with the ganglion cell-inner plexiform and peripapillary retinal nerve fibre layer thinning. These findings suggest that alcohol may play a role in glaucoma severity and progression.

The risk of developing glaucoma in alcohol drinkers was greater than non-alcohol drinkers after adjustment for confounding factors in AD. Wise *et al*<sup>23</sup> also reported a harmful association in a large cohort study of African American women, especially in those consuming  $\geq 7$  drinks/week. In contrast, Kang *et al*<sup>18</sup> found that consumption of  $>30$  g of alcohol per day appeared to be protective against POAG incidence, although this finding did not reach statistical significance. These conflicting reports may potentially be attributed to differences in study populations. For example, Kang *et al*<sup>18</sup> studied populations which were over 90% white—a potential limitation of the study. Also, their study included health professionals, who may not reflect the general population in terms of their education level, access to care, and overall health.<sup>18</sup> Our current study from the DIGS and ADAGES cohort includes a more diverse study population and is more comparable to the Black Women's Health Study (BWHS) by Wise *et al* as it includes a considerable proportion of AD participants. Additionally, similar to Wise *et al*, a harmful association of alcohol consumption was observed in current drinkers.

In the current study, an interaction was found between sex and alcohol consumption and development of

glaucoma. Men who drank alcohol had a higher risk for developing perimetric glaucoma compared with women. A sex-related difference in IOP response has been reported in different populations in which current alcohol consumption was positively related to IOP only in men.<sup>24 37 38</sup> Of note, current alcohol consumption has been shown to be a risk factor for POAG in African American women as well.<sup>23</sup>

Although the pathophysiology has not yet been elucidated, alcohol may directly increase POAG risk. Chronic alcohol use can lead to significant peripheral neuropathy, and the proposed underlying mechanisms may play a similar role in glaucomatous optic neuropathy.<sup>39</sup> Possible mechanisms of chronic alcohol toxicity include oxidative stress leading to free radical damage of neuronal tissue, nutritional deficiencies (especially thiamine), and direct toxic and pro-inflammatory effects. In addition, alcohol may indirectly influence POAG risk through its association with neurodegenerative and cardiovascular diseases. Chronic alcohol use has also been shown to be associated with increased IOP, which may further contribute to POAG risk.<sup>14 15 37 38</sup> Moreover despite the controversy regarding the association of alcohol with ocular hypertension (OHT)<sup>40</sup> and the development of glaucoma,<sup>41</sup> alcohol use was associated with OHT in a study by Leske *et al*<sup>42</sup>

In addition, 110 (18%) of patients are both chronic smokers and alcohol consumers. It is possible that both influence the blood perfusion to the optic nerve head. Alcohol can result in a significant increase in retrobulbar and optic nerve head blood flow<sup>16 43</sup> and retinal artery diameter,<sup>44</sup> but does not appear to have an effect on ocular perfusion pressure.<sup>16 44</sup> Alcohol consumption has been found to be positively associated with both systolic and diastolic blood pressure, which are known to be positively associated with IOP.<sup>45 46</sup> Although many studies have adjusted their analyses for blood pressure or hypertension, residual confounding by various vascular or other risk factors cannot be ruled out.<sup>14</sup>

This study has several limitations. Information on environmental tobacco smoke exposure and use of other types of tobacco was not available for most participants. Also, the amount of alcohol consumption was not considered in the analysis since our questionnaire lacks this information. An important consideration in the interpretation of observational studies of environmental or lifestyle exposures is evidence of a dose-response effect that, if present, supports the hypothesis of a relationship between associated variables. The association between alcohol intake and inner retinal thinning has recently been explored in the UK Biobank. In regular drinkers, alcohol intake was adversely associated with all outcomes in a dose-dependent manner. Restricted cubic spline regression analyses suggested non-linear associations, with apparent threshold effects at approximately 50 g (~6 UK or 4 US alcoholic units)/week for macula retinal nerve fibre layer (mRNFL) and macula ganglion cell-inner plexiform layer (mGCIPL) thickness. In addition,



Mendelian randomisation analyses provided evidence for a causal association with mGCIPL thickness.<sup>47</sup> Future research should aim to define better the dose–response relationship between alcohol or smoking and various glaucoma-related outcomes and traits (including the possibility of a non-linear relationship), as well as the gene–alcohol or gene–smoking interactions supporting these associations. Finally, although the risk of developing glaucoma in smokers was seen to be greater than never smokers after adjustment for confounding factors in older patients (>61 years), our borderline statistical significance should be interpreted cautiously, especially in the presence of multiple testing.

In addition, observational studies investigating the effects of alcohol and tobacco use have several limitations. For instance, reliance on a single self-reported questionnaire to assess alcohol and tobacco use may introduce substantial misclassification bias. Furthermore, these studies may be subject to residual confounding bias, as other unmeasured factors that influence the outcomes of interest may exist. For example, smokers may exhibit lower adherence to medication or engage in other unhealthy behaviours, potentially confounding the outcomes of interest. Moreover, unhealthy diet and lifestyle choices may interact with the variables under investigation in the present study. Additionally, in the present study, smoking and drinking habits were assessed in the middle of the cohort, and changes in the participants' habits over time may affect the accuracy of the results. Physical activities including exercise are also another unmeasured factor that plays a role in glaucoma susceptibility. For example, physical activities have been shown to be associated with less VF loss. Increased walking, longer time spent doing moderate-to-vigorous physical activity, and more time spent in non-sedentary activity were associated with slower rates of VF loss in a treated population of patients with glaucoma.<sup>48</sup> Therefore, physical activity is one of the unmeasured factors in our study which may confound the effect of chronic alcohol consumption or chronic smoking on developing glaucoma

In conclusion, this study demonstrated that alcohol consumption may be a risk factor for glaucoma development in patients with suspected glaucoma, particularly in men and patients of AD. The susceptibility of patients with suspected glaucoma who are smokers to develop perimetric glaucoma is influenced by age, with older smokers at higher risk. As the global burden of glaucoma is increasing, the identification of modifiable risk factors such as smoking and alcohol use may provide an opportunity to improve our understanding of the pathogenesis of glaucoma. Moreover, it can potentially lead to the introduction of preventative measures and treatment strategies beyond IOP reduction. In addition, this provides further evidence to support existing public health strategies aimed at reducing tobacco and alcohol exposure more generally.

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