

ONLINE FIRST

Lifestyle and Risk of Developing Open-Angle Glaucoma

The Rotterdam Study

Wishal D. Ramdas, MD, MSc; Roger C. W. Wolfs, MD, PhD; Albert Hofman, MD, PhD; Paulus T. V. M. de Jong, MD, PhD, FRCOphth; Johannes R. Vingerling, MD, PhD; Nomdo M. Jansonius, MD, PhD

Objective: To determine whether lifestyle-related risk factors, such as socioeconomic status, smoking, alcohol consumption, and obesity, are associated with open-angle glaucoma (OAG).

Methods: Participants from the Rotterdam Study, a prospective population-based cohort study, were considered eligible if they participated at both baseline and follow-up and if they had no OAG at baseline. All participants underwent an identical ophthalmologic examination at all visits, including intraocular pressure measurements, optic nerve head assessment, and perimetry. Lifestyle-related factors were assessed by questionnaires by trained research assistants or measured during the examinations (body mass index and waist to hip ratio). Cox proportional hazard regression analysis was applied to calculate hazard ratios.

Results: Of 3939 eligible participants, 108 (2.7%) de-

veloped OAG during 9.7 years' mean follow-up. No statistically significant effect of socioeconomic status, smoking, or alcohol intake was found. In women, each unit increase in body mass index resulted in a 7% decrease in the risk of developing OAG ($P = .04$). There was a significant increasing effect of body mass index on intraocular pressure ($P < .001$) in women.

Conclusions: Obesity appears to be associated with a higher intraocular pressure and a lower risk of developing OAG. These associations were only present in women. Other lifestyle-related factors, such as socioeconomic status, smoking, and alcohol consumption, were not associated with OAG.

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Author Affiliations:

Departments of Epidemiology (Drs Ramdas, Wolfs, Hofman, Vingerling, and Jansonius) and Ophthalmology (Drs Ramdas, Wolfs, and Vingerling), Erasmus Medical Center, Rotterdam, Department of Ophthalmogenetics, the Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts and Sciences (Dr de Jong), and Department of Ophthalmology, Academic Medical Center (Dr de Jong), Amsterdam, and Department of Ophthalmology, University Medical Center Groningen, University of Groningen, Groningen (Dr Jansonius).

OPEN-ANGLE GLAUCOMA (OAG) is a chronic eye disease characterized by glaucomatous optic neuropathy and corresponding glaucomatous visual field loss. Scientific research has identified several risk factors for OAG. Some of them are modifiable (eg, intraocular pressure [IOP]), whereas others are not (eg, age, sex, myopia, and ethnicity).^{1,2}

A lower socioeconomic status (SES) (income and education) might be a risk indicator for OAG.^{3,4} While SES cannot be changed easily by a patient, some other lifestyle-related risk factors can. Other lifestyle-related risk factors potentially involved in OAG are smoking, alcohol intake, and obesity.^{5,6} Studies on smoking could neither find a clear association with OAG nor with IOP.⁷⁻¹⁰ The same seems to be true for alcohol consumption and OAG,⁷ but interestingly, there is evidence that a higher alcohol intake is associated with a higher

IOP.^{10,11} Similar but apparently conflicting results have been reported on obesity. Obesity has been reported to be inversely related to OAG^{12,13} but positively related to IOP.¹⁴ Especially because the lifestyle-related risk factors smoking, alcohol intake, and obesity are modifiable, these contradicting findings need further evaluation.

The aim of the present study was to determine whether lifestyle-related risk factors are associated with OAG. For this purpose, we used data from the longitudinal population-based Rotterdam Study. Since earlier studies reported conflicting results regarding the effects on OAG and IOP, we investigated the effects on both the incidence of OAG and the IOP.

METHODS

PARTICIPANTS

The Rotterdam Study is a prospective population-based cohort study of residents aged 55

years and older living in a suburb of Rotterdam, the Netherlands. The rationale and study design have been described elsewhere.¹⁵ All measurements were conducted after the medical ethics committee of the Erasmus University had approved the study protocol and all participants had given written informed consent in accordance with the Declaration of Helsinki. The baseline examination took place between 1991 and 1993; follow-up examinations for OAG were performed from 1997 to 1999 and from 2002 to 2006. For this study, we used data from a subset of participants who did not have OAG (see later) at baseline and who completed at least 1 follow-up examination.

OPHTHALMIC EXAMINATION

The examinations at baseline and follow-up included autorefraction (Topcon RM-A2000; Tokyo Optical Co, Tokyo, Japan), keratometry (Topcon OM-4 Ophthalmometer; Tokyo Optical Co), measurement of the best-corrected visual acuity with Early Treatment Diabetic Retinopathy Study optotypes, Goldmann applanation tonometry (Haag-Streit AG, Bern, Switzerland; see later), fundus photography of the posterior pole (Topcon TRC-50VT; Tokyo Optical Co), simultaneous stereoscopic fundus photography of the optic nerve head (Topcon ImageNet System, Topcon TRC-SS2; Tokyo Optical Co), imaging of the optic nerve head with the Heidelberg Retina Tomograph (Heidelberg Engineering, Dossenheim, Germany), and visual field testing (see later).

The IOP was measured at baseline and at every follow-up round. At each visit, 3 measurements were taken on each eye and the median value of these 3 measurements was recorded.¹⁶ In the analysis, we used the higher median of the IOP of both eyes.

The visual field of each eye was screened with a Humphrey Field Analyzer (HFA II 740; Zeiss, Oberkochen, Germany) using a 52-point threshold-related suprathreshold test that covered the central field with a radius of 24°. This test was modified from a standard 76-point screening test.^{17,18} Visual field loss was defined as nonresponse in at least 3 contiguous test points (or 4 including the blind spot). If the first test results were unreliable (>33% false-positive or false-negative responses) or a reliable test result showed visual field loss in at least 1 eye, a second suprathreshold test was performed on that eye. If the second suprathreshold test result was unreliable or showed visual field loss, Goldmann perimetry (baseline and first follow-up)¹⁷ or a full-threshold HFA 24-2 test (second follow-up)¹⁹ was performed on both eyes. The classification process of the Goldmann perimetry test results¹⁷ and the full-threshold HFA 24-2 test results¹⁹ have been described before. In short, visual field loss was considered to be glaucomatous visual field loss only if reproducible and after excluding all other possible causes. Participants were considered to have incident OAG (iOAG) if neither eye had glaucomatous visual field loss at baseline and at least 1 eye showed glaucomatous visual field loss at follow-up.¹⁹

ASSESSMENT OF LIFESTYLE

For SES, we assessed income (salary) and education level separately. Participants were interviewed at baseline by using a questionnaire including questions about their net income (salary minus tax) and education level. For net household income, we used the equivalent household income in Dutch guilders. The value of a Dutch guilder at the baseline of the study roughly equaled that of a dollar in 2010 (using the percentage of change in consumer price index, a measure for economic inflation).²⁰ The equivalent household income was calculated as follows: each participant's household income was classified into 1 of 13

precoded categories. Because in a household more than 1 person would be dependent on a single income, the midpoint of each income category was divided by the number of persons who were living on that income raised to the power 0.36.²¹ This transformation provided the so-called equivalent household income and was analyzed as a continuous variable.²² Education level was categorized in 4 groups according to highest completed education: primary (elementary), lower (vocational/secondary), intermediate (vocational/secondary), and higher (vocational/university).

For smoking, trained research assistants asked participants at baseline about their current and past smoking habits, including type of smoking: cigarette, cigar, or pipe. Smoking was analyzed using nominal categories: never, former, and current smokers.

For alcohol intake, all participants were interviewed at baseline at the study center by a trained dietician using an extensive semiquantitative food frequency questionnaire.²³ Participants reported the number of alcoholic beverages they consumed on a weekly basis in each of the following 4 groups: beer, wine, moderately strong alcoholic beverages such as port wine or sherry, and liquor. For each of these 4 groups, the number of drinks was multiplied by the average amount of ethanol in 1 drink of the alcoholic beverage. A "drink" was defined as 200 mL of beer that contained 8.0 g of ethanol, 100 mL of wine that contained 10.0 g of ethanol, 75 mL of moderately strong alcoholic beverages that contained 10.5 g of ethanol, or 50 mL of liquor that contained 14.0 g of ethanol.²⁴ Earlier studies reported protective effects for persons with a low intake of alcohol on several diseases (eg, cardiovascular diseases) compared with participants with no alcohol intake at all or a high intake. This suggests a U-shaped relation for alcohol consumption.²⁵ Therefore, we analyzed alcohol consumption using nominal categories: no intake and intake less than 10 g, 10 to 20 g, and more than 20 g, after summing the 4 alcohol groups.²⁶

Finally, we studied 2 anthropometric measures related to obesity: body mass index (BMI) and waist to hip ratio.²⁷ The BMI was calculated as weight in kilograms divided by height in meters squared. The waist to hip ratio is a measure of body shape, that is, of relative abdominal obesity. Waist to hip ratio was calculated by dividing waist circumference by hip circumference and expressed as percentages (that is, multiplied by 100). Weight, height, and waist and hip circumference were measured at the research center.

STATISTICAL ANALYSIS

Differences in baseline characteristics between participants with and without iOAG were analyzed with independent *t* tests and χ^2 statistics. Differences in education level were assessed twice, with and without adjustment for myopia. This was done because myopia has been reported to be associated with both education level (as a surrogate measure for near work) and OAG.^{19,28-32} Myopia was stratified into 3 categories by using the spherical equivalent at baseline: high (≤ -4.00 diopters [D]), low (-3.99 to -0.01 D), and no myopia (≥ 0 D). Those eyes with a cataract extraction before baseline were excluded from this analysis. In persons with 1 eye with iOAG, the refraction of that eye was used. In participants without OAG or with OAG in both eyes, the refraction of a random eye was used.

For the multivariate analysis, we used Cox proportional hazard regression analysis to calculate hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) to analyze whether participants had a lower or higher risk of developing OAG. Follow-up duration was used as the time variable. Lifestyle risk factors with $P < .20$ in the univariate comparisons were included in the multivariate analysis. The model was further ad-

Table 1. Characteristics and Univariate Analyses of the Study Population With and Without Incident OAG

	No. (%)		P Value
	Incident OAG (n=108)	No OAG (n=3831)	
Age, y, mean (SD)	67.9 (7.1)	65.2 (6.8)	<.001
Female	53 (49.1)	2248 (58.7)	.05
IOP at baseline, mm Hg, mean (SD)	17.3 (4.7)	15.0 (3.1)	<.001
IOP >21 mm Hg at baseline	13 (12.0)	89 (2.3)	<.001
IOP treatment at baseline	17 (15.7)	88 (2.3)	<.001
IOP at follow-up, mm Hg, mean (SD)	16.5 (4.6)	14.2 (3.2)	<.001
IOP >21 mm Hg at follow-up	14 (13.0)	51 (1.4)	<.001
IOP treatment at follow-up	41 (38.0)	226 (5.9)	<.001
Myopia ^a			
Low	22 (21.0)	770 (20.3)	.67
High	10 (9.5)	186 (4.9)	.03

Abbreviations: IOP, intraocular pressure; OAG, open-angle glaucoma.

^aForty-seven participants were excluded because of cataract surgery before baseline.

justed for age, IOP at baseline, and IOP-lowering treatment and stratified by sex. For the analyses on IOP, we conducted multiple linear regression analyses adjusted for these variables, except for baseline IOP, and stratified by sex.

All statistical analyses were performed using SPSS version 15.0.0 for Windows (SPSS, Chicago, Illinois) and R statistical package version 2.9.1 for Mac (<http://www.r-project.org>). A P value of .05 or less was considered statistically significant.

RESULTS

During a mean follow-up of 9.7 years (range, 5.0-13.9 years), 108 of 3939 participants (2.7%) developed OAG. **Table 1** summarizes the baseline characteristics of the study population according to iOAG status with corresponding univariate comparisons. Participants who developed iOAG during follow-up were significantly older, had more often high myopia, and were more often male compared with those without iOAG.

Table 2 shows the assessed lifestyle risk factors according to iOAG status with corresponding univariate comparisons. At the $P < .20$ level, participants with iOAG had a lower BMI than those without iOAG ($P = .12$). No other differences between participants with and without iOAG were found. The differences in education level between participants with and without iOAG remained insignificant after adjustment for myopia ($P = .49$).

In the multivariate analysis, BMI was associated with a reduced risk of developing iOAG (HR, 0.94 per unit increase in BMI; 95% CI, 0.89-1.00; $P = .03$). After stratification by sex, this association appeared to be only present in women. A higher BMI in women showed a protective effect on OAG (women: HR, 0.93; 95% CI, 0.86-1.00; $P = .04$; men: HR, 0.96; 95% CI, 0.87-1.06; $P = .38$).

Table 3 shows the results of the multiple linear regression analyses with IOP as the outcome measure for all assessed lifestyle risk factors, stratified by sex. None of the assessed variables, except BMI, showed a signifi-

Table 2. Univariate Analyses of Assessed Lifestyle-Related Risk Factors for Participants With and Without Incident OAG

	No. (%)		P Value
	Incident OAG (n=108)	No OAG (n=3831)	
Net monthly household income ($\times 1000$ guilders), mean (SD)	2.2 (0.9)	2.3 (1.0)	.54
Education			
Primary	35 (32.4)	1144 (30.1)	.55
Lower	26 (24.1)	1132 (29.8)	
Intermediate	37 (34.3)	1136 (29.9)	
Higher	10 (9.3)	388 (10.2)	
Smoking			
Never	19 (17.6)	808 (21.3)	.60
Former	53 (49.1)	1719 (45.3)	
Current	36 (33.3)	1269 (33.4)	
Total alcohol intake, g/d, median (IQR)	5.0 (0.4-14.8)	4.3 (0.3-15.4)	.72
Alcohol intake			
No intake	14 (15.4)	588 (17.2)	.40
<10 g/d	50 (54.9)	1574 (46.1)	
10-20 g/d	11 (12.1)	557 (16.3)	
>20 g/d	16 (17.6)	692 (20.3)	
Alcohol intake, g/d, median (IQR)			
Beer	0.3 (0.0-4.7)	0.2 (0.0-3.5)	.27
Wine	0.4 (0.0-1.4)	0.3 (0.0-1.8)	.57
Liquor	5.0 (0.0-14.0)	2.0 (0.0-14.3)	.93
Sherry	1.0 (0.0-6.8)	0.7 (0.0-4.8)	.58
Body mass index, ^a mean (SD)	25.8 (2.9)	26.3 (3.5)	.12
Waist to hip ratio ($\times 100$), %, mean (SD)	89.6 (8.6)	90.0 (9.2)	.69

Abbreviations: IQR, interquartile range; OAG, open-angle glaucoma.

^aCalculated as weight in kilograms divided by height in meters squared.

cant association. Body mass index turned out to have an increasing effect on IOP in women, but not in men.

COMMENT

We did not find any evidence for an association between income, education level, smoking, or alcohol intake and iOAG. We showed in a multivariate analysis that BMI has a protective effect on OAG in women, but not in men. In addition, BMI was associated with a higher IOP in women.

The present findings on SES (income and education level) are in line with those of the Los Angeles Latino Eye Study, which also did not find an association for income or education level with OAG.³³ In contrast, a case-control study of 220 OAG cases found that persons with OAG more often had a lower SES, in terms of having vehicles and owning their houses.³ The current study was based on persons living in a single and rather homogeneous suburb, and as a consequence, the variability in income was limited, making it difficult to find significant associations. Furthermore, mortality rates in persons with lower SES are higher than those with higher SES.³⁴ This effect might have caused an underrepresentation of participants with lower SES in the higher age

Table 3. Multiple Linear Regression Analysis of Lifestyle-Related Risk Factors and Intraocular Pressure Stratified by Sex^a

	Men		Women	
	β (SE)	P Value	β (SE)	P Value
Net household income	0.02 (0.10)	.82	-0.02 (0.08)	.77
Education				
Primary	1 [Reference]		1 [Reference]	
Lower	-0.13 (0.31)	.67	-0.30 (0.18)	.09
Intermediate	0.20 (0.32)	.55	-0.13 (0.20)	.52
Higher	-0.31 (0.30)	.31	-0.65 (0.36)	.07
Smoking				
Never	1 [Reference]		1 [Reference]	
Former	-0.82 (0.38)	.03	0.06 (0.16)	.70
Current	-0.40 (0.49)	.41	-0.22 (0.21)	.29
Body mass index	0.06 (0.04)	.09	0.08 (0.02)	<.001
Waist to hip ratio	0.01 (0.02)	.58	0.01 (0.01)	.46
Alcohol intake				
Beer	-0.01 (0.02)	.58	0.01 (0.06)	.88
Wine	-0.02 (0.05)	.67	-0.001 (0.04)	.98
Liquor	0.01 (0.01)	.18	-0.01 (0.01)	.36
Sherry	0.03 (0.03)	.25	-0.02 (0.01)	.22

^aAll variables adjusted for age and intraocular pressure-lowering treatment.

categories in our population-based cohort. Since OAG is most common in the higher age categories, this might have biased the results.

Studies on the involvement of smoking in IOP or OAG showed conflicting results.^{7,35} A case-control study exploring the relationship between smoking and OAG found a positive association of smoking with OAG.³⁵ In contrast, the Beaver Dam Eye Study did not confirm this association.⁷ Regarding the relationship between smoking and IOP, the Blue Mountains Eye Study reported a modest cross-sectional positive association for current smokers and IOP.^{9,10} A meta-analysis of several epidemiological studies on smoking found a higher risk of developing OAG for current smokers, but not for former smokers.³⁶ However, a large prospective study among more than 100 000 health professionals throughout the United States, which assessed smoking status for more than a decade, found that neither former smokers nor current smokers had an increased risk of developing OAG.³⁷ Nonetheless, the same study reported a borderline inverse association with smoking pack-years.³⁷ A problem in analyzing smoking as a risk factor might be that environmental tobacco smoke cannot be included reliably. Such an exposure misclassification is usually similar in cases and controls and might contribute to a conservative risk estimate. There are scarce data on the possible effect of environmental tobacco smoke on OAG.³⁸

The results of alcohol intake from case-control and prevalence studies are also mixed regarding OAG. Although some studies did not find a significant relationship between alcohol intake and OAG,^{7,33,39,40} others found an association between alcohol intake and IOP, but only in men.^{10,11,41} This was not found in the current study. Also, the insignificant findings when dividing alcohol into groups (beer, wine, liquor, and sherry) are in line with another prospective study.³⁹

Finally, the relationships between BMI and OAG and BMI and IOP seem to be contradictory. In agreement with

our findings, earlier studies found a positive association between BMI and IOP,^{14,42} and other studies suggested an inverse relation of BMI to OAG.^{11-13,43} Of these studies, only the Barbados Eye Study⁴³ and Pasquale et al¹³ mentioned sex effects. The former found a significant association with OAG in men as well as women, and the latter study found for each unit increase in BMI a significant reduction of 6% in the risk of OAG for women, but not for men. This is in line with the present study, which presents a 7% reduction in risk of developing OAG for each unit increase in BMI in women, but no significant effect in men. The Singapore Malay Eye Study, which investigated optic disc parameters, reported a significantly higher BMI in persons with small cup-disc ratios, which also suggests a protective effect of BMI on OAG.^{44,45} We could not find a significant association for BMI with cup-disc ratio, but independent of BMI, a higher waist to hip ratio was significantly associated with a smaller cup-disc ratio (data not shown).

A possible mechanism explaining the inverse association of BMI with IOP regardless of sex could be an increased orbital pressure because of excess fat tissue, with a rise in episcleral venous pressure and a consequent increase in IOP. With obesity, there may also be an increase in the viscosity of blood, with a consequent increase in outflow resistance of the episcleral veins.^{46,47} As mentioned in the "Methods" section, we measured IOP using Goldmann applanation tonometry (mounted on a slitlamp). Interestingly, a study on obese patients (consisting mostly of women) reported a significantly higher IOP when measured with Goldmann applanation tonometry compared with Perkins handheld tonometry, both with patients in a sitting position. This difference was much smaller in the control group.⁴⁸ An explanation for this finding is that, with Goldmann applanation tonometry, the thorax and abdomen are pushed against the slitlamp table while breath holding works like a Valsalva maneuver. This is especially relevant for obese women.

Therefore, measurement of IOP with Goldmann applanation tonometry in women with a high BMI might lead to an overestimation of the actual IOP and as a consequence might contribute to the remarkable relationships between BMI and IOP and BMI and OAG in women. The higher IOP in women with a high BMI should have resulted in an expected higher incidence of OAG. However, this effect was not observed and thus the multivariate analysis yielded a protective effect of BMI on OAG incidence in women. Another explanation might be that high estrogen levels and hormone therapy might be protective to OAG,^{49,50} and obesity seems to be positively related with postmenopausal plasma estrogen levels.⁵¹

Some studies on lifestyle-related risk factors adjusted for cardiovascular-related variables, assuming that these variables may be related to lifestyle and may also have an effect on OAG. Previously, we investigated the relationships between OAG and atherosclerosis and diabetes mellitus but could not find any association.^{52,53} Moreover, adjustment for blood pressure, diabetes mellitus, or cholesterol level did not alter the current results (data not shown).

In conclusion, we could not find an association between SES, smoking, or alcohol consumption and OAG. Although these findings are in line with those from earlier studies, our findings are based on a relatively low number of iOAG cases, and as a consequence, small effects of these lifestyle-related risk factors cannot be ruled out because of power limitations. We found a protective effect of a high BMI on the development of OAG in women. This effect seems to be IOP independent, but an overestimation of IOP as assessed with Goldmann applanation tonometry in obese women may also have contributed to this inverse association.

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Correspondence: Johannes R. Vingerling, MD, PhD, Department of Ophthalmology, Erasmus Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, the Netherlands (j.vingerling@erasmusmc.nl).

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