Risk factors of primary open-angle glaucoma: the first case-control hospital-based study in Vietnam

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Abstract

Purpose: To identify risk factors for primary open-angle glaucoma (POAG) in a Vietnamese population. Methods: A matched case-control study was conducted at Vietnam National Institute of Ophthalmology. Cases were patients clinically diagnosed with POAG. Controls were caregivers of patients with other eye diseases, free from any ocular and systemic abnormalities, and were selected and then matched with the cases by gender and age. Cases and controls were examined by a glaucoma specialist to confirm presence or absence of POAG. Data on demographic, ophthalmic and medical conditions were collected via interview at time of examination. Associations between POAG and potential factors were examined by univariate conditional logistic regression analysis (OR – Odd Ratios) and multivariate conditional logistic regression (AOR – Adjusted Odd Ratios) with level of significance is 0.05. Results: In total, 128 cases with POAG and 128 controls were recruited. Multivariate conditional (fixed-effects) logistic regression analysis resulted in several significant risk factors, including hypertension AOR =4.7 (95% CI: 1.8–12.0; p=0.002); family history of glaucoma AOR = 6.4 (95% CI: 1.3 – 32.2; p = 0.026); over–the–counter eye medication AOR = 3.1 (95% CI: 1.5 – 6.5; p = 0.006), and a protective role for marriage AOR = 0.2 (95% CI: 0.1 – 0.7; p = 0.006) and weekly exercise AOR = 0.3 (95% CI: 0.1 – 0.8; p = 0.021). Conclusions: Hypertension, family history of glaucoma and over–the–counter eye medication were risk factors while marriage and weekly exercise were protective factors for POAG in Vietnamese population.

Background

Glaucoma is globally one of the leading causes of irreversible blindness, and therefore, is a worldwide public health problem. A systemic review and meta–analysis by Tham et al indicated that the prevalence of glaucoma in the population between 40 and 80 of age was 3.54% (95% CI: 2.09 – 5.82). In Africa, primary open angle glaucoma (POAG) was predominant type of glaucoma with a prevalence of 4.20% (95% CI: 2.08-7.35) while the most popular type of glaucoma in Asia was primary angle closure glaucoma (PACG) with 1.09% (95% CI: 0.43-2.32). In 2013, it was projected that the glaucoma population ages from 40 to 80 years would rise to 76 million in 2020, and 118.8 million in 2040. [1]

POAG is considered a silent thief of vision because of its chronic natural course and asymptomatic manifestation. Oftentimes glaucoma patients do not realize their ocular problem until the vision is severely impaired. Therefore, screening and early diagnosis is becoming more vital in glaucoma prevention. In addition to several unchangeable risk factors that have been mentioned in the medical literature such as age and family history of glaucoma [2], modifiable risk factors relating to lifestyle habits are receiving more attention from researchers. To contribute to the knowledge of glaucoma epidemiology in Asia and around the world, we conducted this study to assess select risk factors for POAG in a Vietnamese population.

Methods

This was a matched case-control study conducted in Vietnam National Institute of Ophthalmology (VNIO) from February to June 2016. VNIO is located in Hanoi, the capital of Vietnam, and the catchment area covers the whole North and Middle Vietnam.

Cases

All consecutive patients over 18 years old with newly - diagnosed POAG presenting during the study period were included as cases in the study. The diagnostic criteria of POAG were: the open angle in gonioscopy, without (normal – tension glaucoma) or with intraocular pressure ≧ 22 mmHg, the glaucomatous optic disc change, and the corresponding glaucomatous visual field defect.Intraocular pressure was measured three times in each eye, with the median value documented as the pressure in that eye. Intraocular pressure of a patient was defined as the highest pressure between the two eyes. Glaucomatous optic disc changes included focal or diffuse neuroretinal rim thinning, localized notching, disc hemorrhage and asymmetry between both eyes and retinal nerve fiber layer defects consistent with visual field defects. Glaucomatous visual field defects were confirmed by two of the following three criteria on two consecutive appointments: the presence of a cluster of three points on a pattern deviation probability plot with a probability < 5% in a typical location, one of which had a probability < 1%; a PSD with a probability < 5%; or a glaucoma hemifield test result outside the normal limits.

A glaucomatous diagnostic procedure was carried out by a glaucoma specialist. The indirect ophthalmoscope and funduscopy camera Nidek AFC – 230 with dilation were used for capturing the optic nerve head. Glaucomatous visual field assessment was performed by a Humphrey ^{R} Field Analyzer II – 750i series (24 – 2, SITA; Carl Zeiss Meditec, Dublin, California). The reliability requirement for visual field assessment was fixation loss of 20% or less, false – positive and false – negative responses of 33% or less. Intraocular pressures were measured by Goldmann applanation tomometry. Patients with pseudoexfoliation syndrome, pigmentary dispersion syndrome and other types of secondary glaucoma, cornea diseases as well as any previous ocular surgery or medical history of other eye diseases or systemic diseases that may damage the visual field were excluded from the study.

Controls

Controls adults over 18 years old who were were caregivers of surgically–indicated cataract patients in other departments without glaucoma or ocular hypertension. The selection criteria for control group were: peak intraocular pressure < 21 mmHg, vertical cup to disc ratio < 0.5, cup to disc ratio asymmetry < 0.2, no visual field defect, no medical history of other eye diseases or systemic diseases that may damage the visual field. Controls were assessed by the same glaucoma specialist of the case group with the same protocol and were recruited if they met all inclusion criteria and matched cases by sex and age (± 5 years).

Risk factors

Data on demographic, medical and ophthalmic conditions were obtained through interview and clinical examination. Demographic characteristics included age, gender, education occupation, habitation and marriage. Medical information included diabetes mellitus, hypertension, former and current smoking (> 1 cigarette/day for more than 25 years), alcohol intake (≥ 10 g alcohol/month for ≥ 5 years or more) and weekly exercise (≥ 75 minutes of vigorous – intensity physical activity or ≥ 150 minutes of moderate–intensity physical activity according to 2016 recommendation of WHO).[3] Ophthalmic variables consisted of family history of glaucoma, presence of any refraction errors (myopia, hyperopia and astigmatism), over–the–counter (OTC) ophthalmic medication ≥ 1 time/year and routine eye check < 1 time/2 year.

Statistical analysis

Univariate conditional logistic regression was applied to analyze the association between POAG and potential risk factors. After adjustment for age, factors significantly associated with POAG (level of significance α = 0.05) were included in multivariate conditional logistic regression. Data were analyzed with SPSS online version (provided by The University of Sydney) and SAS statistical software version 9.4 (provided by University of Colorado).

Ethical approval

This study strictly follows the tenets of Declaration of Helsinki. All participants signed the consent forms. The Ethical Committee of Vietnam National Institute of Ophthalmology and Hanoi University of Public Health approved our method.

Results

We recruited 128 cases of POAG and 128 controls into our study. Table 1 shows some demographic characteristics of both cases and controls. There were more males than females, and over 50% of the sample lived in cities. The majority of participants had not received a bachelor degree (81.2% for cases and 74.2% for controls) and had married (79.7% for cases and 90.6% for controls) (Table 1).

(Table 1 would be here)

Table 2 shows characteristics related to behaviors and medical history of study participants. Cases had higher portions of hypertension (43.8% versus 21.9%), smoking (16.4% versus 9.4%), family history of glaucoma (10.9% versus 3.9%), refractive error (35.9% versus 25.8%), OTC eye medication (41.4 % versus 21.9. Cases had lower prevalence of marriage (79.7% versus 90.6%), alcohol intake (28.9% versus 39.1%), weekly exercise (11.7% versus 28.1%) and routine eye examination (62.5% versus 75.8%) compared with the control group.

(Table 2 would be here)

Table 3 demonstrates the univariate analysis of risk factors for POAG. All variables (except age) were then adjusted for age in the analysis procedure. As a result, marriage status, hypertension, alcohol intake, weekly exercise, family history of glaucoma, OTC eye medication and routine eye examination had statistically significant relation to POAG ($p<0.05$). Routine eye examination was no longer significant after adjusting for age ($p=0.170$).

(Table 3 would be here)

Table 4 and figure 1 show results of the multivariate logistic model of risk factors for POAG. Except for alcohol intake ($p = 0.148$), the risk factors remained significantly associated with POAG ($p<0.05$). Indeed, the model demonstrated that people having family history of glaucoma would have 6.4 times of risk for POAG higher than people without this glaucoma history (95% CI: 1.3 – 32.2). Similarly, hypertension people had higher risks for POAG than non-hypertension people (OR=4.7, 95% CI: 1.8 – 12.0) and people with OTC eye medication also had 3.1 times (95% CI: 1.5 – 6.5) of higher risk for POAG than those without OTC eye medication. Having married and weekly exercise are protective factors for POAG as these characteristics had OR less than 1. Figure 1 summaries these results in the forest plot of OR and their 95%CI.

(Table 4 would be here)

(Figure 1 would be here)

Discussion

Primary open angle glaucoma has proven associations with a wide range of factors including intraocular pressure, African–American race and older age especially after the age of 40 years. [2, 4] To the best our knowledge, the present study provided the first comprehensive assessment of glaucoma epidemiology in Vietnam. Vietnam is a typical country of emerging and dynamic Asian economics and it is likely that these results would apply to other similar Asian countries as well. We detected significant associations between POAG and hypertension, family history of glaucoma, OTC eye medication, marriage and weekly exercise.

We found that POAG cases were almost five times more likely than controls to have hypertension compared to controls, which has been mentioned in previous studies conducted in Europe, Australia, China and South East Asia [5-9]. Optic nerve head nutrition is remarkably affected by ocular perfusion pressure (OPP) which relates with systemic blood pressure (mean brachial arterial pressure – MAP) and intraocular pressure (IOP) through the equation $OPP = 2/3.MAP_{brachial} – IOP$.[10] When hypertension is recalcitrant, atherosclerosis will occur and cause the drop of local perfusion pressure. On the other hand, if hypertension treatment is aggressive with day and night medications, patients can suffer from

nocturnal systemic hypotension. In both scenarios, POAG will keep progressing although IOP is well – controlled due to the decreased OPP. This encourages a tight connection between ophthalmologists and cardiologists for a combined follow up.

Not surprisingly, cases were more than six times more likely to have a family history of glaucoma. This classical risk factor has been persistently confirmed through a variety of studies and populations.[11-13] Li et al demonstrated that familial concordant risks were standardized incidence ratio (SIR) = 3.25 (95% CI: 3.16 – 3.35) for POAG.[13] According to O'Brien et al, positive family history was correlated with increased risk of POAG, age–adjusted OR = 3.4 (95% CI: 2.8 – 4.1). [12]. With the evidence of Myocilin mutations in advanced POAG and copy number variations of TBK1 in normal – tension glaucoma, high–risk people should be recommended for family screening for early glaucoma detection. [14, 15]

Our result that OTC eye medication was three times higher among cases than controls is a unique finding from our study. We did not collect details on the specific types of ophthalmic medications that were being used by study participants. We inquired about any OTC eye medications with the exception of saline 0.9% and lubricant. From our experience in Vietnam, the most commonly used OTC eye medication is steroid drops to self-treat red or itchy eye problems. While ophthalmic steroid drops are typically regulated in developed countries like the United States, these medications are often readily available and not regulated in developing countries like Vietnam. In this environment, medications are commonly dispensed by pharmacies without prescription. Although not specifically ophthalmic medication, one study in Hanoi found that although 60% of pharmacy staff reported that they would not dispense corticosteroids, when assessed in practice, 98% of the pharmacies dispensed corticosteroids without a prescription.[16] Almost one-third of patients in our study population had used over-the-counter eye medications at least once in the prior year, which demonstrates how prevalent this issue is in Vietnam. Steroid drops have been shown to increase IOP and induce glaucoma, ocular hypertension, and cataract. Although glaucoma medications are also readily available in Vietnam, awareness and utilization of these medications is much less common and likely does not contribute to this high prevalence of OTC medication in our study. However, due to the lack of specific information on the type of eye medication used, this finding warrants further study.

Our analysis demonstrated that POAG cases were less likely to engage in weekly exercise. This finding was consistent with the benefit of immediate IOP reduction effect after exercises such as walking,[17] running a 42 km marathon [18] and finishing a 110 km march carrying a 20 kg back pack.[19] Some theoretical mechanism involving lowered blood pH, increased blood plasma osmolarity and blood lactate [20], autonomic changes [21] and decreased aqueous production due to dehydration [22] have been introduced. Nonetheless, other evidences have proven other IOP elevation effects of exercise relating to valsava manoeuver, expiratory effort, muscular effort and body position.[23-28] In a recent population–based cross–sectional study, Lin et at found that subjects committed to vigorous exercise 7 days a week had higher risk of having glaucoma than those with three–day exercise per week, and glaucoma was more prevalent in the high intensity of exercise compared to the group of moderate intensity. [29]This disputation could be interpreted that the study of Lin et al had more specific stratifications of physical

activities regarding the number of day per week and the level of intensity whereas our study only examined this factor in general. Taken all together, these studies may suggest that POAG patients should maintain moderate–intensity activities and avoid aggressive exercises, especially those which can induce valsalva effect, however, our study did not delineate between levels of physical activity.

In this study, marriage was significantly more common among controls compared with cases of POAG. This association has been identified in other research as well, with the risk of having open angle glaucoma increased 1.39 times (95% CI: 1.03 – 1.870) in unmarried people in the United States [30] and glaucoma risk perception was significantly associated with marital status in a Ghana study (χ^2 = 41.293, p = 0.0001).[31] Although the reason for this association is not clear, one hypothesis is that this relationship could be because married people have a greater awareness of their disease and/or are given better care from their partners, which may lead to lower prevalence rates of glaucoma. Finally, our study did not show an association between POAG and alcohol intake in multivariate analysis. This result has been confirmed in other studies as well. [32-34]

Our study has several strengths and limitations. One limitation to this research was recall error that could exist for both cases and controls. There is no reason to believe that cases and controls had different recall, therefore this limitation is unlikely to influentially bias our study results. Second, our cases recruited from a hospital which likely sees more severe cases of POAG, therefore, patients may not be representative of all POAG cases in Vietnam. There are some strengths to our study. First, case – control is a suitable design to study risk factors for POAG, an incurable disease with chronic progression that is not too common in Vietnam. Second, Vietnam National Institute of Ophthalmology, as an affiliated hospital of Hanoi Medical University, is one of the best eye care facilities across the country with standardized care, state–of–art equipment and outstanding specialists where the majority of patients in Northern Vietnam visit annually. We also randomly re-input 10% of research forms to ensure the accuracy of our data. In addition, by matching cases and controls, we eliminated confounding by gender, limited confounding by age, and gained efficiency to identify associated risk and preventative factors for POAG. However, matching by age and sex does preclude us from assessing these factors as contributors to POAG risk.

Conclusion

This is the first study that we are aware of that specifically looks at risk factors for POAG in Vietnam. Our study findings indicate that many known risk factors for POAG remain associated with POAG in our Vietnamese population. In addition, we found that use of over-the-counter eye medication is a novel risk factor that warrants more research. In conclusion, our findings enrich the epidemiology knowledge of glaucoma in Vietnam specifically, and in similar countries in Asia. Public health programs in developing regions and countries can benefit from our data to sufficiently tackle the mission of glaucoma screening, primary care and prevention.

Abbreviations

POAG Primary Open-Angle Glaucoma

OR Odds Ratio

AOR Adjusted Odds Ratio

CI Confidence Interval

PACG Primary Angle Closure Glaucoma

VNIO Vietnam National Institute of Ophthalmology

PSD Pattern Standard Deviation

SITA Swedish Interactive Thresholding Algorithm

WHO World Health Organization

OTC Over–the–counter

OPP Ocular perfusion pressure

IOP Intraocular pressure

MAP Mean brachial arterial pressure

Declarations

Ethics approval and consent to participate

The protocol of this study was approved by the Scientific and Ethical Committee in Biomedical Research, Hanoi University of Public Health and Vietnam National Institute of Ophthalmology. All human subjects in the study were asked for their consent before collecting data, and all had complete rights to withdraw from the study at any time without any threats or disadvantages.

Consent for publication

The authors received the consent for publication as a part of ethical approval process of this study.

Availability of data and material

The authors declared that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality

Competing interests

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Authors' contributions

AVB proposed the idea of the study and its design. TTH wrote the first draft of the paper and other authors contributed to add more information into the paper. NBN collected data and participated into data preparation and cleaning. ATKL designed the study and performed data analysis. JLP performed data analysis and drafted the structure of the paper.

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Tables

Table 1. Demographic characteristics of the study population

Characteristics	Cases (n = 128)	Controls (n = 128)	p-values
Age, years (Mean ± SD)	53.6 ± 17.8	51.8 ± 15.1	NA
Gender	70 (54.7%)	70 (54.7%)	NA
Male	58 (45.3%)	58 (45.3%)	
Female			
Education	104 (81.2%)	95 (74.2%)	0.176
≤ High school	24 (18.8%)	33 (25.8%)	
> High school			
Occupation	31 (24.2%)	26 (20.3%)	0.453
Farmer	97 (75.8%)	102 (79.7%)	
Others			
Habitation	72 (56.3%)	65 (50.8%)	0.38
Urban	56 (43.8%)	63 (49.2%)	
Rural			
Marriage	102 (79.7%)	116 (90.6%)	0.014
Yes	26 (20.3%)	12 (9.4%)	
No			

Table 2. Characteristics of behaviors and medical history of the study participants

Characteristics	Cases	Controls	Characteristics	Cases	Controls
	(n = 128)	(n = 128)		(n = 128)	(n = 128)
Diabetes mellitus			*Family history of glaucoma*		
Yes	12 (9.4%)	12 (9.4%)	Yes	14 (10.9%)	5 (3.9%)
No	116 (90.6%)	116 (90.6%)	No	114 (89.1%)	123 (96.1%)
Hypertension			*Refraction error*		
Yes	56 (43.8%)	28 (21.9%)	Yes	46 (35.9%)	33 (25.8%)
No	72 (56.3%)	100 (78.1%)	No	82 (64.1%)	95 (74.2%)
Smoking			*Over-the counter eye medication*		
Yes	21 (16.4%)	12 (9.4%)	Yes	53 (41.4%)	28 (21.9%)
No	107 (83.6%)	116 (90.6%)	No	75 (58.6%)	100 (78.1%)
Alcohol intake			*Routine eye examination*		
Yes	37 (28.9%)	50 (39.1%)	Yes	80 (62.5%)	97 (75.8%)
No	91 (71.1%)	78 (60.9%)	No	48 (37.5%)	31 (24.2%)
Weekly exercise					
Yes	15 (11.7%)	36 (28.1%)			
No	113 (88.3%)	92 (71.9%)			

Table 3. Univariate analysis of risk factors for POAG

Variables	OR	95% CI	p value
Age (years)	1.4	1.2 - 1.5	<0.001
Education (≤ High school)	1.6	0.8 - 3.1	0.153
Occupation (Farmer)	1.3	0.7 - 2.5	0.412
Habitation (Urban)	1.2	0.8 - 2.1	0.379
Marriage (Yes)	0.3	0.1 - 0.8	0.012*
Diabetes mellitus (Yes)	1.0	0.4 - 2.3	1.0
Hypertension (Yes)	3.2	1.7 - 5.9	<0.001*
Smoking (Yes)	2.5	0.9 - 6.4	0.058
Alcohol intake (Yes)	0.5	0.2 - 0.9	0.032*
Weekly exercise (Yes)	0.3	0.2 - 0.7	<0.002*
Family history of glaucoma (Yes)	4.0	1.1 - 14.2	0.032*
Refraction error (Yes)	1.5	0.9 - 2.5	0.109
Over – the – counter eye medication (Yes)	2.2	1.3 - 3.8	0.002*
Routine eye examination (Yes)	0.5	0.3 - 0.9	0.027

*Note: * Statistical significant, after adjustment for age*

Table 4. Multivariate analysis of risk factors for POAG

Characteristics	Adjusted OR	95% CI	p-values
Age (years)	1.4	1.2 - 1.6	< 0.001
Marriage (Yes)	0.2	0.1 - 0.7	0.006
Hypertension (Yes)	4.7	1.8 - 12.0	0.002
Alcohol intake (Yes)	0.5	0.2 - 1.3	0.148
Weekly exercise (Yes)	0.3	0.1 - 0.8	0.021
Family history of glaucoma (Yes)	6.4	1.3 - 32.2	0.026
OTC eye medication (Yes)	3.1	1.5 - 6.5	0.006

Figures

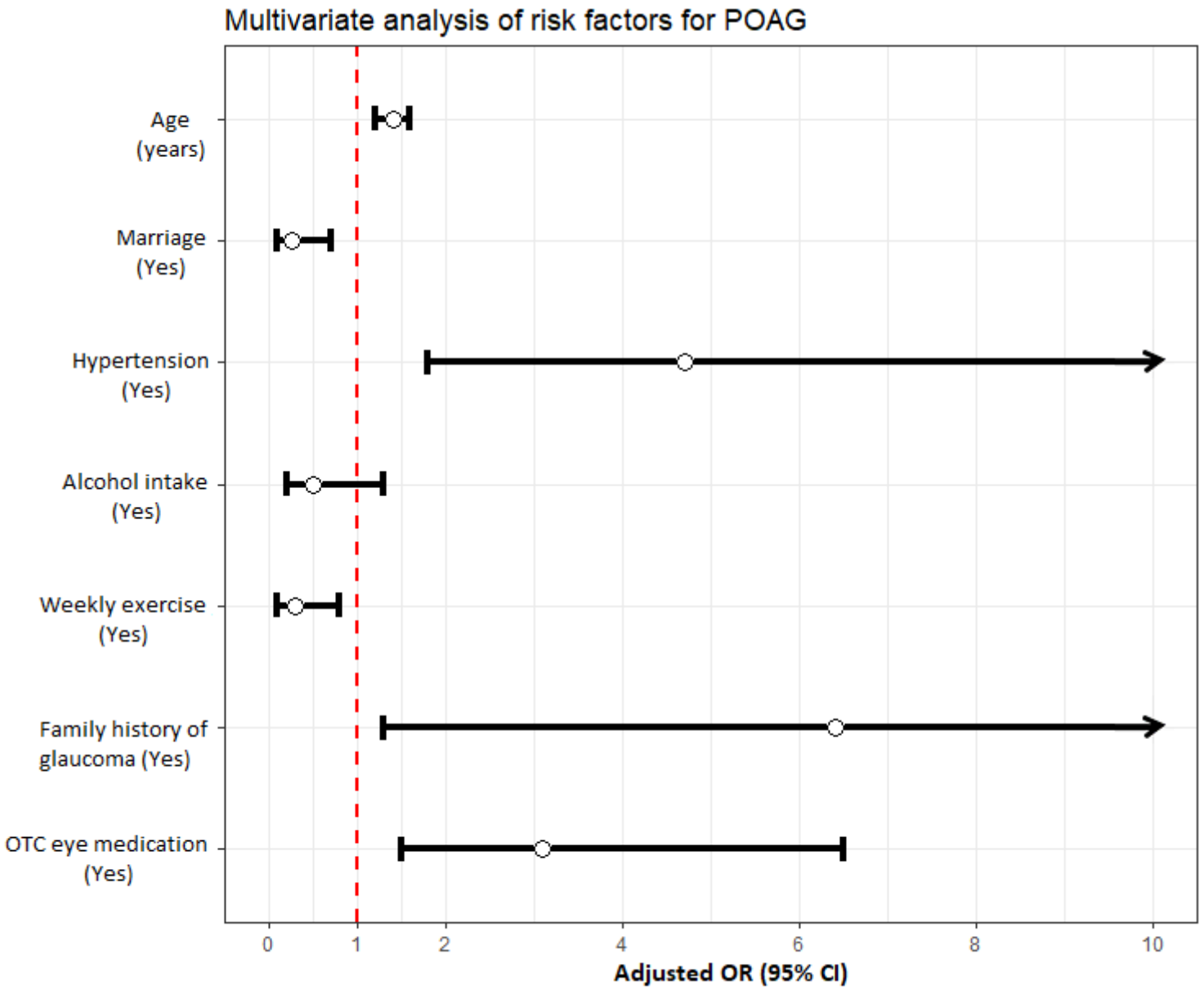

Figure 1

Forest plot of ORs in multivariate analysis of risk factors for POAG