

Underweight increases the risk of primary open-angle glaucoma in diabetes patients

A Korean nationwide cohort study

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Abstract

The impact of underweight on the risk of developing primary open-angle glaucoma (POAG) is not known, although the association between obesity and POAG has been well studied. We evaluated the risk of POAG among underweight patients by studying a nationwide cohort sample in South Korea.

We analyzed data from the Korean National Health Insurance Research Database collected between 2009 and 2012 for 17,000,636 patients aged 40 years or older. Newly diagnosed POAG in the cohort was identified using claims data between 2009 and 2015.

A total of 442,829 individuals (2.60%) were classified as underweight (body mass index [BMI] < 18.5 kg/m²). During the follow-up period, 435,756 (2.56%) subjects were newly diagnosed with POAG. Multivariate analyses revealed that underweight was significantly related to an increased risk of future POAG development, by 9.8% and 27.8% in individuals with and without diabetes, respectively. There was a reverse J-shaped relationship between BMI and risk of POAG in the normal, impaired glucose tolerance, and diabetes groups; especially, this relationship was most notable in participants with diabetes.

Patients who were underweight exhibited a significantly higher prospective risk of POAG, even after adjusting for confounding factors.

Abbreviations: AF = atrial fibrillation, BMI = body mass index, CVD = cardiovascular disease, HR = hazard ratios, ICD = International Classification of Diseases, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, IOP = intraocular pressure, KHANES = Korea National Health and Nutrition Examination Survey, KNHIS = Korean National Health Insurance Service, NHIC = National Health Insurance Corporation, POAG = primary open-angle glaucoma.

Keywords: body mass index, cohort studies, diabetes mellitus, glaucoma, Korea, underweight

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Précis: We analyzed data from the Korean National Health Insurance Research Database and found that underweight patients have a higher risk of developing primary open-angle glaucoma.

The authors have no conflicts of interest to disclose.

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1. Introduction

Glaucoma is a multifactorial disease characterized by optic nerve cupping and visual impairment and is the most common cause of irreversible blindness worldwide.^[1] Primary open-angle glaucoma (POAG) makes up the majority of glaucoma cases. Well-known risk factors for this condition include old age, high intraocular pressure (IOP), African ethnicity, high myopia, and a family history of glaucoma.^[2–4] Some studies have reported that cardiovascular factors, such as obesity, metabolic syndrome, and diabetes, are also associated with the development of POAG or high IOP.^[5–7] However, inconsistent results were reported for analyses of subjects with limited ranges of age, sex, and ethnicity.

Whereas obesity has been considered a public health threat,^[8–10] the health impacts of underweight have received comparatively less attention. However, there is growing evidence that underweight also has significant negative health effects and increases the risk of mortality.^[11–14] Some researchers have suggested an “obesity paradox,” in which obese individuals with cardiovascular disease survive longer than their normal-weight counterparts.^[15] With respect to ocular diseases, relationships between obesity and cataract, age-related macular degeneration, POAG, and pterygium have been reported.^[16,17] However, to date no studies have evaluated the role of underweight in eye diseases. Smoking, drinking, and underlying pre-existing disease may be confounding factors when analyzing the hazardous effects of underweight on mortality and morbidity.^[18,19] Underweight could merely be a consequence of chronic illness or a behavioral/psychological condition. Therefore, it is necessary

to adjust for factors that can influence weight change to assess associations between underweight and adverse health outcomes.^[12,20,21]

Notably, the majority of previous studies investigating the effects of underweight have been conducted using Caucasian cohorts, for whom only a small proportion of the population is underweight. Hence, most of these studies did not differentiate between underweight and normal-weight patients in their analyses, or had a statistical power too small to detect differences in risk of developing POAG for this specific group. In Asia, where the general population tends to be leaner and underweight is highly prevalent, understanding the health outcomes associated with underweight has become particularly important.^[22,23]

Recently, several population-based studies in South Korea have reported that low body mass index (BMI) may be associated with an increased risk of developing high IOP and POAG. However, these results are limited in their ability to suggest causality, due to their cross-sectional study designs.^[12,24] Additionally, there have been no reports of an association between underweight and the risk of developing POAG. Therefore, we investigated the relationship between underweight and the prospective risk of POAG development, using health claims data from a nationwide cohort sample of 17,000,636 South Korean individuals in the National Health Insurance Corporation (NHIC) database, which includes approximately 97% of the South Korean population.^[25]

2. Materials and methods

2.1. Statement of ethics

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Korean National Health Insurance Service (KNHIS). The study design was also reviewed and approved by the Institutional Review Board of St. Mary's Hospital, Seoul, South Korea. The need for obtaining written informed consent from participants was waived by the institutional review board.

2.2. Data source and study population

Detailed information regarding the history, contents, and acceptable use of data in the NHIC database has been described previously.^[25,26] Briefly, the KNHIS provides access to its databases for investigating longitudinal observation of the South Korean population health status, with limited permission. To access NHIC data, researchers are required to pay a fee and have the study approved by the official review committee. Because national health insurance is a fee-for-service system used to pay health-care providers, the database contains information regarding patients' demographics and medical history, insurers' payment coverage, and patients' deductions and claims (diagnosis/prescriptions/consultation statements). Each patient is identified by a social identification number given at birth; therefore, no healthcare records of the patients were duplicated or omitted. Patients in the NHIC are recommended to undergo biennial standardized medical examinations.

The examination data for this study included measurements of height, weight, blood pressure, and serum laboratory tests. When multiple examinations occurred during the follow-up period, only data from the first examination was analyzed. We included subjects who underwent health examinations provided by the

NHIC between January 2009 and December 2012. Out of the 32,165,883 individuals aged 40 years and over, those who had missing baseline data ($n=674,398$), multiple examinations ($n=14,292,801$), or pre-existing diabetes ($n=198,048$) were excluded from the analysis. Remaining 17,000,636 individuals were included in the analysis. The primary endpoint of this study was newly diagnosed POAG and included all patients who received glaucoma medication during the study period (between 2009 and 2015) with at least 2 visits for either inpatient or outpatient care for POAG, defined according to the International Classification of Diseases, 10th revision (ICD-10) code H401.

BMI was calculated as weight in kilograms, divided by the square route of height in meters (kg/m^2). Patients were categorized into 5 BMI groups: underweight, BMI $< 18.5 \text{ kg}/\text{m}^2$; normal, BMI $18.5\text{--}22.9 \text{ kg}/\text{m}^2$; overweight, BMI $23.0\text{--}24.9 \text{ kg}/\text{m}^2$; obese class I, BMI $25.0\text{--}29.9 \text{ kg}/\text{m}^2$; and obese class II, BMI $> 30.0 \text{ kg}/\text{m}^2$. The definition of hypertension was based on the ICD-10 codes I-10, I-13, and I-15; and included patients who were taking hypertension medication, and had a systolic blood pressure over 140 mm Hg and diastolic blood pressure over 90 mm Hg. Diabetes was defined under ICD-code E11–14, and included patients taking diabetes medications and with fasting glucose levels $> 126 \text{ mg}/\text{dL}$. Hyperlipidaemia was defined using ICD-code E78, and included patients taking cholesterol-lowering medication, with serum total cholesterol $> 240 \text{ mg}/\text{dL}$.

2.3. Statistical analysis

A Cox proportional hazards model was used to evaluate the association between underweight and prospective POAG. Multivariable regression analyses were performed using the BMI categories described above. The variables used for regression models included age, sex, smoking status, alcohol consumption, exercise frequency, hypertension, diabetes, monthly household income, and dyslipidaemia. Model 1 was adjusted for age and sex; model 2 was adjusted for age, sex, exercise frequency, smoking status, alcohol consumption, monthly household income, diabetes mellitus, hypertension and dyslipidaemia. Statistical analyses were performed using SAS statistical software version 9.2 (SAS Institute, Cary, NC) and R statistical programming software version 3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria, <http://www.R-project.org>). A 2-tailed P value $< .05$ was considered statistically significant.

2.4. Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

3. Results

Among a total of 17,000,636 enrolled individuals, 447,877 (2.60%) subjects were classified as underweight, and 5,231,084 (30.8%) and 606,096 (3.57%) subjects were classified as obesity classes I and II, respectively (Table 1). These BMI groups differed significantly in terms of demographics, lifestyle, monthly household income, and systemic medical status. The cohort was followed up for a period of between 1 and 7 years (median 5.5 years). During the observation period, 435,756 (2.56%) subjects were newly diagnosed with POAG.

Table 1
Characteristics of the study population according to the body mass index levels.

	Body mass index (kg/m ²)					P value
	<18.5 (n=442,829)	18.5–23 (n=6,284,405)	23–25 (n=4,436,222)	25–30 (n=5,231,084)	30– (n=606,096)	
Sex (male)	177,461 (40.07)	2,594,656 (41.29)	2,262,259 (51)	2,836,050 (54.22)	253,500 (41.83)	<.0001
Smoking						<.0001
Never smoker	292,866 (66.14)	4,248,105 (67.6)	2,781,274 (62.69)	3,167,063 (60.54)	408,253 (67.36)	
Ex-smoker	39,886 (9.01)	729,987 (11.62)	728,164 (16.41)	956,042 (18.28)	83,883 (13.84)	
Current smoker	110,077 (24.86)	1,306,313 (20.79)	926,784 (20.89)	1,107,979 (21.18)	113,960 (18.8)	
Drinking						<.0001
None	302,016 (68.2)	3,874,105 (61.65)	2,552,657 (57.54)	2,942,445 (56.25)	378,000 (62.37)	
Mild to moderate	120,850 (27.29)	2,092,028 (33.29)	1,601,685 (36.1)	1,885,851 (36.05)	183,533 (30.28)	
Heavy	19,963 (4.51)	318,272 (5.06)	281,880 (6.35)	402,788 (7.7)	44,563 (7.35)	
Daily exercise, yes	169,301 (38.23)	2,979,052 (47.4)	2,236,435 (50.41)	2,601,766 (49.74)	272,508 (44.96)	<.0001
Income, lowest Q1	127,464 (28.78)	1,693,247 (26.94)	1,121,955 (25.29)	1,315,237 (25.14)	169,518 (27.97)	<.0001
Diabetes mellitus	31,208 (7.05)	509,208 (8.1)	514,603 (11.6)	814,908 (15.58)	140,340 (23.15)	<.0001
Hypertension	85,241 (19.25)	1,428,625 (22.73)	1,455,896 (32.82)	2,299,720 (43.96)	361,959 (59.72)	<.0001
Dyslipidemia	48,151 (10.87)	1,073,582 (17.08)	1,087,195 (24.51)	1,596,999 (30.53)	229,406 (37.85)	<.0001
Age (years)	55.8±14	53.2±11.2	54.2±10.6	54.5±10.6	53.5±10.7	<.0001
Height (m)	160.5±8.6	161.1±8.4	162±8.8	162.2±9.2	160.6±9.6	<.0001
Weight (kg)	45.4±5.4	55.4±6.7	63.1±7.1	70.7±8.6	82.6±10.5	<.0001
BMI (kg/m ²)	17.6±0.9	21.3±1.2	24±0.6	26.8±1.3	31.9±2	<.0001
Waist circumference (cm)	67.6±6	74.9±6.2	81.4±5.8	87.4±6.3	96.6±7.5	<.0001
Systolic blood pressure (mm Hg)	117.3±16	120.2±15.3	124.3±15	127.7±15	131.9±15.5	<.0001
Diastolic blood pressure (mm Hg)	73.1±10.2	74.7±10	77.1±9.9	79.3±10	82±10.4	<.0001
Serum glucose (ng/mL)	95.3±24.3	96.7±23	100.1±24.7	103.3±26.4	108.3±30.1	<.0001
Serum high lipoprotein (ng/mL)	61.5±17.7	57.8±16.9	54±16.5	51.9±16.5	51.1±16.3	<.0001
Serum cholesterol (ng/mL)	186±34.8	194.2±35.8	200.2±37.1	203.2±38	205.4±39.3	<.0001

Data are expressed as number (percentage) or mean ±SD.

Underweight patients had a significantly increased risk of developing POAG after adjustment for baseline factors, that is, age, sex, smoking status, alcohol intake, exercise frequency, monthly household income, diabetes, hypertension, and dyslipidemia (Table 2). Compared to patients of normal weight (BMI between 18.5 and 23 kg/m²), the relative risk of developing POAG increased by 12.9% for underweight patients and decreased by 3.4%, 6.0%, and 8.0% for class I and class II obese patients, respectively.

We further analyzed prospective risk of POAG development by comparing patients within BMI groups with and without diabetes (Table 3). Compared with normal patients, diabetes in underweight patients significantly increased their risk of future POAG development, in fact an increase by 9.8% and 27.8% was reported in individuals without diabetes and with diabetes, respectively. Conversely, obesity classes I and II were associated with a 2.2% and 3.9% decrease, respectively, in prospective risk

of developing POAG in individuals without diabetes, and a 19.5% and 22.8% decrease, respectively, in the prospective risk of POAG in individuals with diabetes. One interesting thing to notice is that there was not a substantial increased risk of POAG development in patients with extremely high BMI (both diabetic and nondiabetic patients). Since there exist little of extremely high BMI individuals in Korea, additional studies would be helpful to analyze western population.

BMI and prospective risk of POAG presented a reverse J-shaped relationship (Fig. 1), which was more obvious in diabetic subjects. Lower BMI significantly increased the risk of POAG development, whereas extremely high BMI also increased risk. The risk of underweight was more apparent in patients with diabetes. Additionally, we calculated hazard ratios (HR) according to body weight and diabetes, with respect to obese individuals without diabetes. The prospective risk of POAG was greatest in underweight patients in all groups, including those

Table 2
Multivariate regression analysis for development of newly diagnosed primal open-angle glaucoma.

BMI (kg/m ²)	N	Patient*year	Incidence	HR (95% CI)	
				Model 1	Model 2
<18.5	7218	2217328.48	3.25527	1.047 (1.022,1.072)	1.129 (1.102,1.157)
18.5-23	82,426	33106504.45	2.48972	Reference	Reference
23-25	63,047	23679305.82	2.66254	1.025 (1.015,1.036)	0.966 (0.956,0.977)
25-30	76,614	27812754.98	2.75464	1.051 (1.041,1.061)	0.94 (0.93,0.949)
30-	8435	3146749.93	2.68054	1.121 (1.096,1.146)	0.92 (0.899,0.941)

N denotes subject numbers; BMI=body mass index, CI=confidence interval, HR=hazard ratio.

Model 1 =adjusted for age and sex.

Model 2 =adjusted for for age, sex, exercise frequency, smoking status, alcohol consumption status, monthly income, diabetes, hypertension, and dyslipidemia.

Table 3
Risk of primary open-angle glaucoma (POAG) according to the body mass index (BMI) classification in diabetic and nondiabetic subjects.

	N	Non-DM		N	DM	
		HR (95% CI)			HR (95% CI)	
		Model 1	Model 2		Model 1	Model 2
BMI (kg/m ²)						
<18.5	411,621	1.053 (1.025,1.081)	1.098 (1.069,1.127)	31,208	1.207 (1.139,1.279)	1.278 (1.205,1.354)
18.5–23	5,775,197	Reference	Reference	509,208	Reference	Reference
23–25	3,921,619	1.023 (1.011,1.036)	0.99 (0.978,1.002)	514,603	0.903 (0.883,0.923)	0.872 (0.853,0.892)
25–30	4,416,176	1.038 (1.026,1.05)	0.978 (0.967,0.99)	814,908	0.858 (0.84,0.875)	0.805 (0.789,0.822)
30–	465,756	1.049 (1.02,1.079)	0.961 (0.934,0.988)	140,340	0.852 (0.82,0.885)	0.772 (0.743,0.802)

N denotes subject numbers; BMI=body mass index, CI=confidence interval, DM=diabetes mellitus, HR=hazard ratio.

Model 1=adjusted for age and sex.

Model 2=adjusted for age, sex, exercise frequency, smoking status, alcohol consumption status, monthly income, diabetes, hypertension and dyslipidemia.

without diabetes, impaired fasting glucose (IFG), and with diabetes (Fig. 2). Notably, a more than 2-fold increase in risk of developing POAG was found for patients who were underweight and had diabetes (HR=2.219, IR=2.096–2.349).

4. Discussion

The relationship between underweight and POAG has not been analyzed in previous studies, and to our knowledge, this is the first population-based study to independently evaluate the effect of underweight on the development of POAG. Our study showed that underweight was significantly related to prospective risk of developing POAG. Also, we showed that underweight was related to a low socio-economic status, frequent smoking, less alcohol intake, and chronic systemic diseases, which may also be risk factors for POAG development. However, we found that underweight still had a significant effect on POAG development,

even after adjusting for these confounding factors. Interestingly, the additive risk of developing POAG was higher for underweight individuals with diabetes. In contrast, being overweight or obese was associated with a lower risk for POAG. In this study, we found that the underweight group comprised 2.6% of the South Korean population, making it possible to analyze them as a separate group. The mean BMI for the United States or Europe was reported to be approximately 30kg/m², compared with 24 kg/m² for the present study population.^[8,27,28]

The results of previously published epidemiologic studies comparing BMI, IOP, and POAG are inconsistent and contradictory. In previous reports, obesity has been inversely related to POAG, but positively correlated with IOP. For example, in the Rotterdam study, a prospective population-based cohort study comprising of 3939 participants, 2.7% of subjects developed POAG during the mean 9.7 years of follow-up.^[29] They reported that the risk of POAG decreased by 7% for each

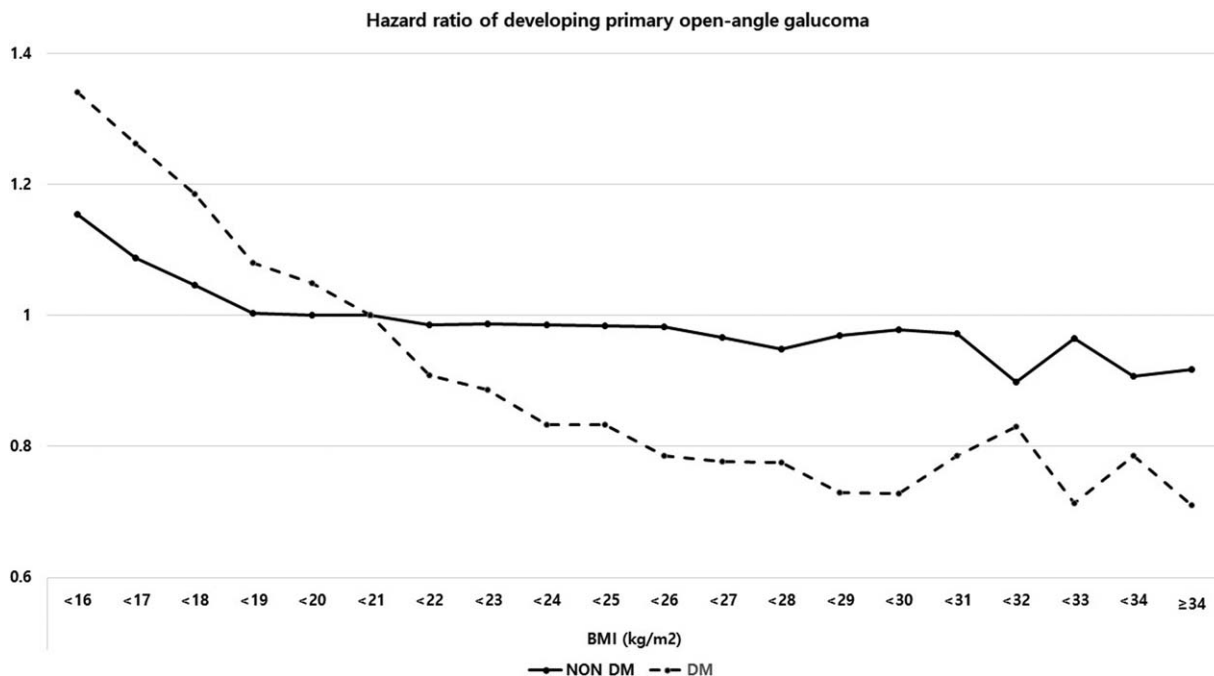


Figure 1. Multiple regression analysis of prospective risk of primary open-angle glaucoma (POAG) according to body mass index (BMI). BMI and prospective risk of POAG presented a reverse J-shaped relationship, more obvious found in diabetic subjects.

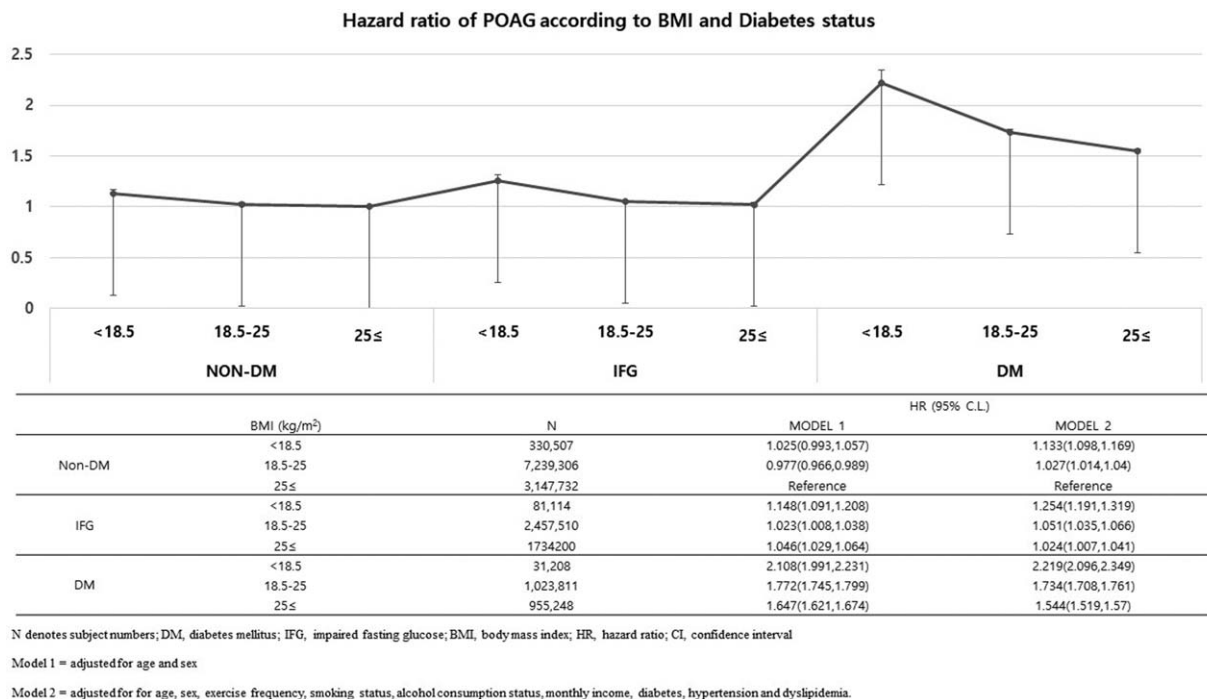


Figure 2. Multiple regression analysis of prospective risk of primary open-angle glaucoma (POAG) according to body mass index and diabetes status. Hazard ratios (HR) are shown according to body weight and diabetes, with respect to obese individuals without diabetes. Note that the prospective risk of POAG was greatest in underweight patients in all groups, including those without diabetes, impaired fasting glucose (IFG), and with diabetes.

unit increase in BMI, but only in women. However, there was a significant increase in the risk of elevated IOP with increasing BMI, despite elevated IOP being a risk factor for POAG. These contradictory results have not been fully explained. However, a possible explanation for the positive association between BMI and IOP could be increased orbital pressure due to excessive fat tissue. Obesity can cause increased blood viscosity, which may result in increased outflow resistance and episcleral venous pressure. The Korea National Health and Nutrition Examination Survey (KHANES) analysis concluded that high fat mass was associated with lower prevalence of POAG, which could explain the contradictory effects of obesity on IOP and development of POAG.^[24] A later Rotterdam study, with a follow-up period of median 11.1 years, found that BMI had a nonsignificant protective effect on POAG development.^[30] However, this study had the combined limitations of follow-up loss and a relatively small sample size. The Singapore Malay Eye study, a cross-sectional study of 3280 patients of Malay ethnicity, reported a significantly higher BMI for persons with a small cup:disc ratio, which may also suggest a protective role for obesity against POAG development.^[31] The Beijing Eye study, another Asian population-based cross-sectional study, concluded that degree of fundus tessellation, which is known to be associated with POAG, was significantly higher in elderly males with lower BMI.^[32] However, no previous studies analyzed the effect of underweight on the prospective risk of developing POAG in a large cohort.

Significant evidence now suggests that not only obesity, but also underweight, is harmful to health.^[15] Although obesity is a well-known major risk factor for cardiovascular disease (CVD), it seems to confer a survival advantage once CVD occurs. Similar findings are known for type 2 diabetes, in which overweight patients showed a significantly lower mortality rate compared

with those of normal weight.^[33] Other researchers have found a close association between impaired glucose tolerance (IGT) and BMI, which was equal in both underweight and obese participants.^[34] Likewise, BMI was shown to have a U-shaped relationship with the risk of atrial fibrillation (AF).^[27] This paradoxical association between BMI and systemic disease mortality raises the possibility that a similar obesity paradox might exist in the pathogenesis of POAG.

One possible explanation for the harmful effects of underweight is the deprivation of adipose tissue, which has a beneficial effect on metabolism.^[35] The level of adiponectin, an adipocyte-derived factor, is increased in underweight individuals and decreased in obese individuals. It has been suggested that lower levels of adiponectin in obese individuals could heighten the risk of AF.^[36] However, previous reports have shown that higher, not lower, levels of adiponectin are independently associated with an increased risk of AF in older adults, despite its documented cardiometabolic benefits.^[24,37] A second potential factor linking is the muscle mass and arterial stiffness. Arterial stiffness increases with age and also known to be associated with low muscle mass.^[38,39] Previous study showed that an increased arterial stiffness was shown to be associated with glaucoma, and might contribute to the pathogenesis of glaucoma in diabetes patients.^[40] We assume that low muscle mass, which would be reflected by low BMI, may be significantly associated with systemic arterial stiffness and glaucoma.

A major strength of this study is that the KNHIS database contains a large cohort, which covers 97% of the population of South Korea.^[25] Based on the national health screening program, the KNHIS data contains information regarding demographic factors, health care utilization, health threatening risk factors, and other health-related behaviors.^[26] The comprehensive

administrative information from KNHIS regarding health care utilization for each subject prevents recall bias. Furthermore, the long-term observation period made use of consistent definitions and included data on relevant confounding factors that could influence the risk of POAG development. Still, the utilization of this database for our study has some inherent limitations. All individuals in the South Korean population with medical insurance are entitled to biennial medical evaluations; however, not all patients undergo regular check-ups. There may also be a selection bias because individuals who undergo regular medical examinations are generally more aware of their health status. However, the participation in this examination program was shown to be high as 74.8% in 2014.^[25] Additionally, we acknowledge the possibility of undetected POAG, since the diagnosis of POAG was defined based on ICD codes, which may be less accurate than the diagnostic criteria employed by medical chart review-based studies. Moreover, in most cases early POAG is asymptomatic; hence, some new cases may not have been detected within the follow-up period, whereas pre-existing asymptomatic cases may have only been diagnosed after the study commenced. Lastly, although we found a statistically significant relationship between underweight and POAG development, further evidence is required in the form of interventional studies to establish a conclusive causative relationship between underweight and POAG.

In conclusion, this study found that patients who were underweight exhibited a significantly higher prospective risk of POAG, even after adjusting for confounding factors, including age, sex, smoking status, alcohol uptake, exercise frequency, household income, diabetes, hypertension, and hyperlipidaemia. The pathophysiology underlying underweight as a risk factor for POAG needs to be evaluated in future studies.

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