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Anthropometric Measures and their Relation to Incident Primary Open-Angle Glaucoma

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Abstract

Purpose—To assess the relation between anthropometric measures and incident primary open-angle glaucoma (POAG).

Design—Prospective cohort study.

Participants—We included 78,777 women in the Nurses Health Study and 41,352 men in the Health Professionals Follow-up Study.

Methods—Females and male health professionals were prospectively followed during the periods 1980–2004 and 1986–2004, respectively. Eligible participants were 40+ years old, did not have POAG at baseline and reported receiving eye examinations during follow-up. Information regarding anthropometric measures, potential confounders and ophthalmic status was updated using biennial questionnaires. During follow-up, 980 self-reported POAG cases were confirmed with medical record review.

Main outcome measures—Multivariable rate ratios (MVRR) of POAG and their 95% confidence intervals [95% CI].

Results—There was no significant relation between cumulatively averaged body mass index (BMI) in kg/m^2 and POAG overall (p for trend = 0.06). However, in relation to POAG with intraocular pressure (IOP) < 22 mm Hg at diagnosis, each unit increase in BMI was associated with a 6% reduced risk in women (MVRR = 0.94 [0.91–0.98]; p=0.01) but not for men (MVRR = 1.02 [0.96–1.09]; p=0.57); this gender difference was significant (p-heterogeneity =0.03). In multivariable analyses to explore the independent effects of height and weight, weight (as height-adjusted weight residuals; p for trend = 0.002), but not height (p for trend = 0.10) appeared to account for most of the inverse association between BMI and POAG with IOP ≤ 21 mm Hg at

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diagnosis in women. There was no association between BMI and POAG with IOP > 21 mm Hg at diagnosis for either gender (p for trend ≥ 0.26). Among women, analyses found that the relations between anthropometric parameters and the two POAG subtypes (POAG with IOP ≤ 21 mm Hg versus POAG with IOP > 21 mm Hg when diagnosed) were significantly different (p ≤ 0.0001).

Conclusions—Among women, higher BMI was associated with a lower risk of POAG with IOP ≤ 21 mm Hg at diagnosis. The factors contributing to this tendency may yield insight into the pathogenesis of POAG.

Primary open-angle glaucoma (POAG) is a progressive optic neuropathy that produces permanent visual loss. The level of intraocular pressure (IOP) is strongly implicated in the pathogenesis of POAG.[1–3] In the Baltimore Eye Survey, an IOP of 35 mm Hg was associated with a 39-fold higher risk of POAG compared with an IOP < 15 mm Hg.[2] Nonetheless, there is significant overlap in IOP between people with and without POAG,[4, 5] suggesting that other factors also contribute to neuronal degeneration in this disorder.

Body mass index (BMI) is positively associated with type 2 diabetes mellitus[6] - a complex disorder of glucose metabolism. Both higher BMI[7–13] and diabetes mellitus (DM)[8, 12, 14–18] are associated with modest elevations of IOP. Whether the positive associations between BMI and IOP translate into reduced aqueous humor outflow facility that could produce POAG is unclear. While increasing central corneal thickness (CCT) may contribute to the positive association between DM and IOP,[19, 20] other mechanisms may also be at work. One population-based study found that DM was independently associated with increased IOP, even after controlling for CCT and other factors.[12] Reports on the relation between DM and POAG itself have been inconsistent. While several studies found that DM was positively associated with POAG,[17, 21–24] others reported no association.[16, 25–29]

The inter-relations between BMI, IOP, DM and open angle glaucoma are complex in nature. Given the immense public health consequences of obesity, it is important to assess the relation between anthropometric measures and POAG. However, few cross-sectional and prospective studies have been conducted.[23, 25, 30] The objective of this study is to report on the relation between anthropometric measures and incident POAG a longitudinal cohort study of 41,352 men and 78,777 women followed for at least 18 years.

METHODS

Description of the cohort at risk for primary open-angle glaucoma

The Nurses' Health Study (NHS) is an ongoing population-based cohort of registered nurses. The NHS was established in 1976 when 121,700 US women were invited to complete a questionnaire regarding lifestyle, health behavior and chronic diseases. The Health Professionals Follow-Up Study (HPFS) is an ongoing cohort created in 1986 when 51,529 male healthcare providers (dentists, veterinarians, pharmacists, optometrists, osteopaths, and podiatrists) completed a similar health survey. The participants in both cohorts have been followed biennially with mailed questionnaires that have updated health and lifestyle information. The observation period for this study was 1980 – 2004 for women and 1986 – 2004 for men. The Human Research Committees of Brigham & Women's Hospital, Massachusetts Eye and Ear Infirmary and the Harvard School of Public Health approved this study.

Participants were excluded from the study at baseline (defined as 1980 in NHS and 1986 in HPFS) for the following reasons: 1) 23,239 women in NHS who did not respond to the initial 1980 semiquantitative food frequency questionnaire (SFFQ) as the relation between diet and POAG was the initial objective of this study, 2) 5,994 women and 1,596 men with inadequate dietary information on the SFFQ (for women adequate dietary information

consisted of > 50 of 61 items completed yielding 500–3500 kcal/day, while > 61 out of 131 items completed with a total caloric intake range of 800–4200 kcal/day was regarded as adequate for men), 3) 3,624 women and 1,927 men who reported cancers aside from nonmelanoma skin cancer prior to a glaucoma diagnosis as a cancer diagnosis could profoundly affect anthropometric measures, 4) 801 women and 808 men who indicated a diagnosis of glaucoma or glaucoma suspect at baseline, 5) 739 women and 1,084 men lost to follow-up immediately after baseline, and 6) 6,466 women and 3,903 men who never reported an eye exam during follow-up. After these exclusions, 80,837 women and 42,211 men remained. At each two-year period, we applied additional provisional exclusions for participants who were under age 40, did not report having had an eye exam in the previous two years and were missing data on height and weight. In the first two-year risk period, 17,045 women and 234 men who were < 40 years old, 18,859 women and 12,213 men who did not report an eye exam and 34 women and 597 men who were missing data on height and weight were excluded, leaving 44,899 women and 29,146 men eligible. At later periods, the ineligible participants at the first 2 years entered the cohort, if they reached 40 years of age, reported receiving eye exams and provided data on height and weight. Hence by 2004, 78,777 women and 41,352 men contributed person-time. Follow-up rates through 2004 were high (> 85% of the total possible person-time).

Eligibility for the eye exam criterion was determined by selecting those who responded positively to the question of whether an eye exam was received in the previous two years. For example, if a HPFS participant answered positively only in 1996 and 1998, then he contributed person-time only during 1994–96 and 1996–1998 cycles. Because this question was first asked in 1990 in both cohorts, eye exam eligibility was determined this way from the risk period 1988–1990 and onwards. For the initial periods 1980–88 in NHS and 1986–88 in HPFS, eye exam eligibility was based on responses to the 1990 question. Participants contributed person-time until death, loss to follow-up, a diagnosis of cancer other than nonmelanoma skin cancer, a self-report of glaucoma or the end of the study (2004).

Case ascertainment and validation—We adopted a POAG case-identification method feasible for large cohorts whose members are geographically dispersed. Detailed description of our case identification method has been previously described.31 Briefly, we evaluated medical records including visual field (VF) data from participants with a self-report of glaucoma in a standardized manner to identify POAG cases. Our POAG case definition is predicated on the presence of two abnormal, but reliable VFs consistent with a nerve fiber layer defect in the context of slit lamp biomicroscopic findings showing no secondary cause for elevated IOP and posterior segment findings suggesting no other cause for VF loss. Our case confirmation method has been found to be valid and highly specific. For construct validity of our case confirmation method, we previously showed that African American heritage and a self-report of a positive family history of glaucoma were risk factors for POAG in NHS and HPFS.[31] In addition, we reviewed the medical records from 50 participants whose self-report of glaucoma was refuted (not POAG) by their eye care provider. A systematic review of these records showed no evidence of POAG, substantiating the accuracy of claims made by the eye care providers.

During the study period, 5,809 women and 2,529 men reported that they had been diagnosed with glaucoma. The eye doctors confirmed this diagnosis in 67% of women and 58% of men as follows: POAG with VF loss (29% women; 27% men), only elevated IOP or optic disc cupping (19% women; 20% men) and other types of glaucomas or glaucoma suspect (19% women; 11% men). The remaining 33% of self-reports in women and 42% in men could not be confirmed, as the participants themselves (6% women; 11% men), or their eye doctors (4% women; 5% men) could not be contacted, participants did not give permission to review their records (10% women; 11% men), participants indicated the initial report was in error

(11% women; 14% men) or participants' eye doctors refuted the diagnosis of POAG (2% women; 1% men).

Of the 1,680 women and 695 men confirmed to have POAG with VF loss by their doctors, 642 women and 338 men met criteria for POAG and were included in the analyses.

Anthropometric Measures—We asked about height and weight at baseline in NHS (1980) and HPFS (1986); weight was then updated biennially in each cohort. We also asked participants to recall their weight in young adulthood at baseline (weight at age 18 for women and weight at age 21 for men). We calculated body mass index (BMI) as weight in kilograms divided by height in meters squared. We also calculated change in BMI from young adulthood. When weight data was missing for any 2-year study interval we carried forward the value from the prior available cycle.

We collected information about hip and waist circumference in 1986 for women and in 1987 for men (using a supplemental questionnaire). We asked participants to measure their waist at the umbilicus and their hips at the largest circumference between the waist and thighs while standing and to avoid making such measurements while wearing bulky clothes. These measures were repeated in 1986, '96, '00 and '04 in NHS and in '86 and '96 in HPFS. We provided a tape measure and an illustration to standardize the measurement process. Sixty-five percent of the men and 73% of women provided this data.

Trained technicians assessed the precision of the self-reported measures of weight and body size. They obtained these measurements directly in a subset of NHS and HPFS study participants. The Pearson correlation between self-reported measures and the average of the technician values ranged from 0.84 to 0.97 for all measures.[32] In a related cohort (Nurses Health Study II), recalled weight at age 18 among women who were 25 to 42 years old was highly correlated with measured weight in the medical records at entry to college or nursing school (r = 0.87).[33] In another cohort, recalled past body weights were also highly correlated with past measures.34 Self-reported height in middle-aged adults aged is generally regarded as sufficiently valid for analytical analysis.33, 35, [36]

Statistical Analysis

As glaucoma is a slowly developing condition, we chose to study cumulatively averaged anthropometric measures as they best represent long-term measures. We calculated cumulatively updated BMI by averaging the reports from all questionnaires up to the start of each 2-year period at risk. We also evaluated BMI in young adulthood and change in BMI from young adulthood.

BMI is a composite measure of weight and height, but in glaucoma, the independent effects of height and weight may also be of interest. Thus, to further explore the independent relations of weight and of height with POAG, we first formed a regression model of weight on height,[37] to calculate weight residuals that were centered at the median weight values (141 lbs for women and 154 lbs for men). Then, the resulting weight residuals (which are uncorrelated with height) and height were entered in a multivariable model to assess their relation with POAG. Finally, we evaluated the associations with hip circumference, waist circumference and hip to waist circumference ratio in relation to POAG risk.

For statistical analyses, we first calculated incidence rates of POAG by dividing the incident cases by the person-years accrued for each category of anthropometric measure. We adjusted for age using 5-year categories, and calculated Mantel-Haenszel age-adjusted incidence rate ratios (RR) and their 95% confidence intervals (CIs). Then for multivariable analyses, we controlled for potential glaucoma risk factors by including them

simultaneously in Cox proportional hazards analysis stratified by age in months and the specific 2-year period at risk.[38] We conducted tests for trend by including the midpoint values within each category. Variables considered for inclusion were family history of glaucoma, African-American heritage (yes / no), pack years of smoking, physical activity (quartiles of activity intensity/day), cumulatively updated caffeine consumption (g/day) and alcohol intake (g/day). Cumulatively updated intakes of alcohol and caffeine intake (in quintiles) were determined from SFFQs administered every 2–4 years starting in 1980 in NHS and 1986 in HPFS. In alternate models, we also controlled for a self-report of hypertension and DM, which may lie in the pathways by which anthropometric measures may alter the risk of POAG.

We first analyzed the data from each cohort separately and performed tests for heterogeneity of the cohort specific results to check for appropriateness of pooling the results. Then, we pooled the results using meta-analytic methods incorporating random effects.[39] In secondary analyses, we assessed the anthropometric measures in relation to risk of subtypes of POAG: "high-tension" and "normal tension" POAG defined as those cases with maximum IOP > 21 mm Hg or IOP ≤ 21 mm Hg, respectively, at diagnosis. Using these cutoffs, 32.5% of all POAG cases had IOP ≤ 21 mm Hg at diagnosis. We used a competing risk survival analysis to compare the associations of anthropometric measures with high-tension glaucoma versus normal tension glaucoma.[40] Joint modeling of associations with related outcomes allows for explicit comparisons of the associations of a risk factor with these different outcomes. Likelihood ratio tests were used to evaluate the evidence for the similarity of associations.

Results

During 1,610,334 person-years of follow-up, we identified 980 incident POAG cases. As expected, participants with higher BMI had higher rates of hypertension and DM (Table 1). They were also less likely to be physically active or consume alcohol or smoke cigarettes. We accounted for these potential confounders in multivariable analyses.

Compared with the reference group of cumulatively averaged BMI in the 24 – 25 kg/m^2 range (Table 2), there were no significant associations with very low BMI (MVRR = 1.15 [0.93 – 1.41] for BMI < 22 kg/m^2) or high BMI (MVRR = 0.98[0.76 – 1.26] for BMI ≥ 30 kg/m^2) in relation to overall POAG; the inverse trend between higher BMI and POAG risk was not significant (p = 0.06). These results were not materially altered when hypertension and DM were additionally controlled for in the multivariable models (data not shown).

There were no associations between cumulatively averaged BMI and POAG subtypes (high tension or normal tension subtype). However, when we examined associations by gender (Table 2), there was a significant inverse linear trend between cumulatively averaged BMI and POAG with IOP ≤ 21 mm Hg at VF loss in women whereby every unit increase in BMI was associated with a 6% reduced risk of normal tension POAG subtype (MVRR = 0.94 [0.91 – 0.98]; p = 0.001); however, there were no such association with the normal tension POAG variant in men (MVRR = 0.98 [0.90 – 1.05]; p = 0.52). The p for heterogeneity between women and men for the association between linear BMI and the normal tension POAG subtype was significant (p = 0.03). In addition, among women, the relation between linear BMI and normal tension POAG was significantly different from the relation between linear BMI and high tension POAG (p < 0.0001). Again, these results remained unchanged when additional controls for hypertension and DM were introduced (data not shown).

Linear BMI during young adulthood (age 18 in women and age 21 in men) was not related to POAG overall (MVRR = 0.98 [0.95 – 1.02]). However, in relation to POAG with IOP ≤ 21 mm Hg at diagnosis, we observed inverse relations with linear BMI among women

(MVRR = 0.92 [0.87 – 0.97]; p = 0.003) but not among men (MVRR = 1.05 [0.97 – 1.13]; p = 0.25; p-heterogeneity = 0.009). Change in BMI from young adulthood was not associated with POAG overall or the POAG subtypes.

We examined the independent effects of weight (uncorrelated with height) and of height with POAG (Table 3). We found an inverse relation between weight residuals (adjusted for height) and POAG. Those with the highest weight residuals (≥ 162.2 lbs in women and ≥ 194.2 lbs in men) had a 24% lower risk of POAG (MVRR = 0.76 [0.61 – 0.94]; p-for-trend = 0.008) compared with those with the lowest weight residuals (<124.7 lbs in women and <161.2 lbs in men). There was no relation between weight residuals and POAG with IOP > 21 mm Hg at diagnosis. In contrast, there was a significant inverse association between weight residuals and the normal tension POAG subtype in women but not men. Among women, the difference in the associations between weight residual terms and the POAG subtypes was also statistically significant ($p < 0.0001$). The results did not change in models that also included hypertension and diabetes (data not shown). We found no significant relations of height with POAG overall or with the POAG subtypes (Table 4).

To further explore whether the distribution of weight is important, we examined waist and hip circumferences. Conceptually, total body mass consists of adipose and lean tissue, with the latter consisting of total body water, muscle and bone. Waist circumference reflects adipose tissue predominantly while hip circumference reflects both adipose as well as lean tissue. Participants with the largest hip circumference had a 27% lower risk of POAG overall versus participants with smallest hip circumferences (MVRR = 0.73 [0.53 – 1.00]) (Table 5). The inverse association was also notable for the high-tension POAG subtype and no gender differences were noted. Finally, we found no relation between waist circumference and POAG overall (data not shown) or the POAG subtypes.

Discussion

In this prospective study, we did not observe associations between cumulatively averaged BMI and POAG overall. Interestingly, we found significant inverse relations between higher BMI and POAG with IOP ≤ 21 mm Hg among women, but not among men. Height was not associated with risk of POAG. The trends reported here are consistent with prior cross-sectional data,[25, 30] although the gender-specific nature of the trend has not been previously reported. The significant inverse association we observed between BMI and POAG is a secondary outcome derived after our study population was stratified by gender and level of IOP when VF loss occurred and the result should be interpreted cautiously.

It is remarkable that increasing BMI is not positively related to POAG given the association of BMI with IOP,[7–13] the relation between obesity and DM,[6] and the potential positive influence of DM on IOP[8, 12, 14–18, 41] and on POAG.[17, 21–24] In fact, we found an inverse relation between higher weight uncorrelated with height and normal tension POAG among women (p = 0.002). While the inverse association between weight residuals and normal tension POAG among women could be due to chance, it is reasonable to entertain biological mechanisms that might support such an association. Perhaps some measure linked to adiposity or lean mass that is under sex hormonal influences may protect against the development of POAG. It is possible that higher circulating estrogen levels in postmenopausal women with higher BMI[42–46] bind to estrogen receptors expressed on retinal ganglion cells[47, 48] to mediate neuroprotection. Interestingly, a population-based study in Singapore found that lower BMI and male gender was associated with greater vertical cup-disc ratio.[49] Adipose tissue does serve as an endocrine organ,[50] and may secrete other paracrine factors that could also influence retinal ganglion cell health. Finally, the fact that body mass index at age 18 was associated with POAG risk suggests that correlates of

early life exposures may be important in disease etiology. Results from the Sydney Childhood Eye Study indicating that low birth weight was associated larger cup-disc ratio in 12-year-old children is consistent with the assertion that early life exposures could be related to POAG.[51]

One limitation of this study is that anthropomorphic measures were self-reported. Correlations between self reported weight and measured values were generally very high ($r > 0.95$)[32] in our population, but participants tended to slightly underestimate their weight. This systematic bias is unlikely to affect the estimates of the relative rates. There should not be differential reporting of anthropometric measures by POAG case status, especially since the anthropomorphic data were collected prospectively, before participants' diagnosis of POAG. While obese patients might be more likely to be under ophthalmic surveillance as they are at higher risk of DM and diabetic eye disease, we did not find a positive relation between BMI and POAG. Although we restricted the study to participants who reported receiving eye exams, there was almost certainly some under-detection of POAG in our cohorts, as participants did not undergo standardized eye exams. However, it is unlikely that differences in under ascertainment could have explained our findings of inverse associations with BMI and the normal tension POAG subtype in women. Thus, although there are limitations related to the self-reporting of anthropomorphic measures and the outcome of POAG, we believe that these potential biases do not explain our results.

Another limitation of this study is that the generalizability of the results might be limited, because our participants were mostly European-derived Caucasians. In one study of an African population residing in Barbados, Leske et al. concluded that lean body mass was also associated with POAG in men and women.[25] We did not control for CCT in this study, but it is not clear whether adjusting for CCT might have altered the study results. One study that reported on the relation between BMI and CCT found a null association.[52]

Overall, our study has several strengths. The data on anthropometric measures were prospectively collected for more than 18 years and for cases of POAG, the exposures were assessed before the diagnosis of POAG. Anthropometric measures and methods of POAG ascertainment have been validated, and analyses were adjusted for many key covariates including age, African ancestry, family history of glaucoma, hypertension and DM. We performed a comprehensive survey of body composition and POAG that included an assessment of remotely recalled BMI and change in BMI from young adulthood.

In conclusion, in this predominately Caucasian population, we found an inverse trend between cumulatively averaged BMI and incident POAG with IOP ≤ 21 mm Hg at diagnosis among women. The most important measure driving this relation appears to be weight, independent of height. Weight uncorrelated with height may be an important covariate in studies of POAG that develops at IOP ≤ 21 mm Hg. Determining the mechanisms of how anthropometric measures may influence the risk of POAG may unlock important clues regarding disease pathogenesis.

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Table 1

Age and age standardized characteristics according to cumulatively updated body mass index

		Categories of cumulatively updated body mass index (kg/m^2)					
		<22	**22–24**	**24–26**	**26–28**	**28–30**	**30+**
Age (mean, yr)	Women	56.0	57.7	58.9	59.4	59.5	58.9
	Men	60.4	60.2	60.6	60.9	60.7	60.3
African Americans (%)	Women	0.5	0.8	1.3	1.5	1.7	1.7
	Men	0.4	0.5	0.6	0.7	1.1	1.0
Hypertension (%)	Women	20.7	26.6	33.4	40.7	48.7	60.2
	Men	32.1	38.3	45.1	53.2	59.1	69.3
Diabetes (%)	Women	1.8	2.4	3.7	6.3	9.4	17.8
	Men	4.8	5.5	7.8	10.9	16.3	28.4
Highest quartile of physical activity (%)	Women	30.4	27.1	23.8	20.9	19.0	15.1
	Men	29.5	29.9	27.0	23.7	20.7	16.0
Current smokers (%)	Women	19.5	16.5	15.2	14.6	13.0	11.0
	Men	7.8	5.6	6.1	6.2	6.6	6.2
Mean alcohol intake (g/d)	Women	7.5	7.0	6.1	5.1	4.4	3.2
	Men	10.0	10.7	11.3	11.2	11.5	10.1
Mean caffeine intake (mg/d)	Women	326	334	337	332	318	300
	Men	195	213	236	254	258	265
Family history of glaucoma (%)	Women	13.2	12.8	12.5	12.7	12.6	12.3
	Men	11.1	11.1	10.6	10.5	9.9	9.8
Number of reported eye exams	Women	5.3	5.3	5.3	5.3	5.2	5.1
	Men	4.7	4.8	4.8	4.8	4.8	4.7

* Age-standardized characteristics over the entire follow-up period, using 5-year intervals of age

Table 2

Cohort specific and pooled analyses of body mass index (kg/m^2) in relation to risk of primary open-angle glaucoma (POAG), high tension POAG (intraocular pressure > 21 mm Hg) and normal tension POAG (intraocular pressure ≤ 21 mm Hg)

ALL PRIMARY OPEN ANGLE GLAUCOMA:					
Cumulatively averaged BMI	**NHS cohort**		**HPFS cohort**		
	# Cases	**MVRR†**	**# Cases**	**MVRR†**	**Pooled MVRR†**
<22	165	1.19 [0.94 – 1.52]	30	1.01 [0.66 – 1.55]	1.15 [0.93 – 1.41]
22–23.9	162	1.15 [0.91 – 1.46]	77	1.03 [0.76 – 1.40]	1.10 [0.91 – 1.33]
24–25.9	118	**REFERENCE**	104	**REFERENCE**	**REFERENCE**
26–27.9	80	1.02 [0.77 – 1.36]	76	1.13 [0.83 – 1.53]	1.07 [0.87 – 1.32]
28–29.9	41	0.83 [0.58 – 1.18]	29	0.84 [0.55 – 1.29]	0.83 [0.63 – 1.10]
30+	76	1.04 [0.77 – 1.39]	22	0.83 [0.52 – 1.35]	0.98 [0.76 – 1.26]
P for trend		0.09		0.48	0.06
Linear BMI		0.99 [0.97 – 1.01]; p = 0.15		0.99 [0.95 – 1.03]; p = 0.54	0.99 [0.97 – 1.00]; p = 0.12
POAG WITH INTRAOCULAR PRESSURE > 21 mm Hg AT VISUAL FIELD LOSS:					
Cumulatively averaged BMI	NHS cohort		HPFS cohort		
	# Cases	MVRR†	# Cases	MVRR†	Pooled MVRR†
<22	107	1.21 [0.89–1.64]	21	0.95 [0.58–1.57]	1.13 [0.88 – 1.47]
22–23.9	99	1.12 [0.82–1.52]	55	0.97 [0.68–1.39]	1.05 [0.84 – 1.33]
24–25.9	73	**REFERENCE**	79	**REFERENCE**	**REFERENCE**
26–27.9	50	1.04 [0.72–1.49]	55	1.09 [0.76–1.55]	1.06 [0.82 – 1.37]
28–29.9	29	0.97 [0.63–1.50]	20	0.79 [0.48–1.31]	0.89 [0.6 – 1.24]
30+	56	1.26 [0.89–1.80]	13	0.70 [0.38–1.26]	0.99 [0.55 – 1.76]
P for trend		0.91		0.26	0.62
Linear BMI		1.01 [0.98–1.03]; p = 0.53		0.98 [0.93–1.02]; p = 0.26	1.00 [0.97 – 1.03]; p=0.82
POAG WITH INTRAOCULAR PRESSURE ≤ 21 mm Hg AT VISUAL FIELD LOSS:					
Cumulatively averaged BMI	NHS cohort		HPFS cohort		
	# Cases	MVRR†	# Cases	MVRR†	Pooled MVRR†

ALL PRIMARY OPEN ANGLE GLAUCOMA:					
Cumulatively averaged BMI	**NHS cohort**		**HPFS cohort**		
	# Cases	**MVRR†**	**# Cases**	**MVRR†**	**Pooled MVRR†**
<22	58	1.16 [0.78 – 1.72]	9	1.23 [0.55 – 2.79]	1.17 [0.82 – 1.68]
22–23.9	63	1.21 [0.82–1.78]	22	1.22 [0.67–2.20]	1.21 [0.88–1.68]
24–25.9	45	**REFERENCE**	25	**REFERENCE**	**REFERENCE**
26–27.9	30	0.99 [0.62 – 1.58]	21	1.20 [0.65 – 2.19]	1.06 [0.73 – 1.54]
28–29.9	12	0.60 [0.32 – 1.14]	9	1.04 [0.48 – 2.26]	0.76 [0.45 – 1.28]
30+	20	0.68 [0.40 – 1.16]	9	1.19 [0.52 – 2.69]	0.82 [0.49 – 1.37]
P for trend		**0.01**		0.88	**0.04**
Linear BMI		**0.94 [0.91–0.98]; p = 0.001**		1.02 [0.96–1.09]; p = 0.57	0.98 [0.90–1.05]; p = 0.52‡

*Cohort-specific results were pooled using random effects.

BMI=body mass index; NHS=Nurses' Health Study; HPFS=Health Professionals Follow-Up Study

†MVRR=Multivariate relative risk adjusted for age (years), family history of glaucoma, African American heritage, smoking (0,1–9, 10–19, 20–29, 30+ pack years), physical activity (quartiles of Met-hours/week), cumulatively updated alcohol intake (0, <5, 5–14, 15–29, 30+ g/d).

‡The p for heterogeneity between women and men was significant (p=0.03). In all other instances, the p for heterogeneity was >0.05.

Table 3

Cohort specific and pooled analyses of cumulative weight residuals in relation to risk of primary open-angle glaucoma (POAG), high tension POAG (intraocular pressure > 21 mm Hg) and normal tension POAG (intraocular pressure ≤ 21 mm Hg)

ALL PRIMARY OPEN ANGLE GLAUCOMA:						
Category in pounds: NHS	**NHS cohort**		**Category in pounds: HPFS**	**HPFS cohort**		**Pooled MVRR†**
	# Cases	**MVRR†**		**# Cases**	**MVRR†**	
<124.7	124	**REFERENCE**	<161.2	69	**REFERENCE**	**REFERENCE**
124.7 – 134.2	128	0.90 [0.70 – 1.15]	161.2 – 171.3	76	1.13 [0.80 – 1.58]	0.97 [0.78 – 1.21]
134.3 – 145.2	132	0.84 [0.66 – 1.08]	171.3 – 180.8	65	0.91 [0.64 – 1.29]	0.86 [0.70 – 1.05]
145.3 – 162.1	137	0.82 [0.64 – 1.05]	180.8 – 194.2	73	1.06 [0.75 – 1.49]	0.90 [0.71 – 1.15]
162.2+	121	0.72 [0.56 – 0.93]	194.2+	55	0.84 [0.58 – 1.22]	0.76 [0.61 – 0.94]
P for trend		**0.01**			0.31	**0.008**
Linear BMI		1.00 [0.99 – 1.00]; p = 0.13			1.00 [0.99 – 1.00]; p = 0.60	1.00 [1.00 – 1.00]; p = 0.12
POAG WITH IOP > 21 mm Hg AT VISUAL FIELD LOSS:						
Category in pounds: NHS	NHS cohort		Category in pounds: HPFS	HPFS cohort		Pooled MVRR†
	# Cases	MVRR†		# Cases	MVRR†	
<124.7	78	**REFERENCE**	<161.2	53	**REFERENCE**	**REFERENCE**
124.7 – 134.2	84	0.95 [0.69 – 1.30]	161.2 – 171.3	50	0.91 [0.61 – 1.36]	0.93 [0.73 – 1.19]
134.3 – 145.2	85	0.88 [0.64 – 1.20]	171.3 – 180.8	51	0.92 [0.61 – 1.37]	0.89 [0.70 – 1.14]
145.3 – 162.1	77	0.75 [0.55 – 1.04]	180.8 – 194.2	54	1.00 [0.68 – 1.48]	0.85 [0.64 – 1.12]
162.2+	90	0.90 [0.66 – 1.23]	194.2+	35	0.71 [0.46 – 1.11]	0.83 [0.65 – 1.08]
P for trend		0.40			0.22	0.17
Linear BMI		1.00 [1.00–1.00]; p = 0.61			1.00[0.99–1.00]; p = 0.31	1.00[1.00–1.00]; p = 0.85
POAG WITH IOP ≤21 mm Hg AT VISUAL FIELD LOSS:						
Category in pounds: NHS	NHS cohort		Category in pounds: HPFS	HPFS cohort		Pooled MVRR†
	# Cases	MVRR†		# Cases	MVRR†	
<124.7	46	**REFFERENCE**	<161.2	16	**REFFERENCE**	**REFFERENCE**
124.7 – 134.2	44	0.81 [0.53 – 1.23]	161.2 – 171.3	26	2.04 [1.05 – 3.95]	1.24 [0.50 – 3.06]

ALL PRIMARY OPEN ANGLE GLAUCOMA:						
Category in pounds: NHS	**NHS cohort**		**Category in pounds: HPFS**	**HPFS cohort**		
	# Cases	**MVRR†**		**# Cases**	**MVRR†**	**Pooled MVRR†**
134.3 – 145.2	47	0.78 [0.52 – 1.18]	171.3 – 180.8	14	0.88 [0.41 – 1.86]	0.80 [0.56 – 1.15]
145.3 – 162.1	60	0.91 [0.62 – 1.35]	180.8 – 194.2	19	1.18 [0.58 – 2.40]	0.97 [0.69 – 1.36]
162.2+	31	0.45 [0.28 – 0.72]	194.2+	20	1.29 [0.63 – 2.62]	0.74 [0.26 – 2.05]
P for trend		**0.002**			0.98	0.19
Linear BMI		**0.99 [0.98–1.00]; p = 0.001**			1.00 [0.99–1.01]; p = 0.59	1.00 [0.98–1.01]; p = 0.50‡

*Cohort-specific results were pooled using random effects.

†MVRR=Multivariate relative risk adjusted for age (years), family history of glaucoma, African American heritage, smoking (0,1–9, 10–19, 20–29, 30+ pack years), physical activity (quartiles of Met-hours/week), cumulatively updated alcohol intake (0, <5, 5–14, 15–29, 30+ g/d), height (6 categories).

BMI=body mass index; IOP=intraocular pressure; NHS=Nurses' Health Study; HPFS=Health Professionals Follow-Up Study

‡The p for heterogeneity between women and men was significant (p=0.02). In all other instances, the p for heterogeneity was >0.05.

Table 4

Cohort specific and pooled analyses of adult height in relation to risk of primary open-angle glaucoma (POAG), high tension POAG (intraocular pressure > 21 mm Hg) and normal tension POAG (intraocular pressure ≤ 21 mm Hg)

ALL PRIMARY OPEN ANGLE GLAUCOMA:						
Category in inches: NHS	**NHS cohort**		**Category in inches: HPFS**	**HPFS cohort**		**Pooled MVRR†**
	# Cases	**MVRR†**		**# Cases**	**MVRR†**	
<62	147	**REFERENCE**	48–67	44	**REFERENCE**	**REFERENCE**
62.1 – 63.9	79	0.99 [0.75 – 1.30]	67.1 – 68.9	85	1.47 [1.00 – 2.14]	1.18 [0.80 – 1.75]
64 – 65.9	205	1.02 [0.83 – 1.27]	69 – 70.9	69	1.73 [1.17 – 2.56]	1.30 [0.78 – 2.17]
66 – 66.9	88	1.01 [0.77 – 1.32]	71 – 72.9	84	1.42 [0.97 – 2.06]	1.17 [0.84 – 1.62]
67+	123	1.04 [0.82 – 1.33]	73+	56	1.63 [1.07 – 2.47]	1.27 [0.82 – 1.95]
P for trend		0.72			0.03	0.23
Linear height		1.00 [0.97–1.03]; p = 0.99			1.02 [0.98–1.06]; p = 0.39	1.01 [0.98–1.03]; p = 0.59
POAG WITH INTRAOCULAR PRESSURE > 21 mm Hg AT VISUAL FIELD LOSS:						
Category in inches: NHS	NHS cohort		Category in inches: HPFS	HPFS cohort		Pooled MVRR†
	# Cases	MVRR†		# Cases	MVRR†	
<62	98	**REFERENCE**	48–67	34	**REFERENCE**	**REFERENCE**
62.1 – 63.9	51	0.95 [0.68 – 1.34]	67.1 – 68.9	57	1.32 [0.85 – 2.05]	1.09 [0.80 – 1.48]
64 – 65.9	142	1.04 [0.80 – 1.35]	69 – 70.9	49	1.59 [1.01 – 2.51]	1.24 [0.82 – 1.85]
66 – 66.9	46	0.78 [0.55 – 1.11]	71 – 72.9	65	1.43 [0.93 – 2.21]	1.04 [0.58 – 1.89]
67+	77	0.95 [0.70 – 1.28]	73+	38	1.48 [0.91 – 2.41]	1.13 [0.74 – 1.74]
P for trend		0.44			0.10	0.70
Linear BMI		0.98 [0.94–1.02]; p = 0.35			1.01 [0.96–1.07]; p = 0.59	0.99 [0.96–1.03]; p = 0.71
POAG WITH INTRAOCULAR PRESSURE ≤ 21 mm Hg AT VISUAL FIELD LOSS:						
Category in inches: NHS	NHS cohort		Category in inches: HPFS	HPFS cohort		Pooled MVRR†
	# Cases	MVRR†		# Cases	MVRR†	
<62	49	**REFERENCE**	48–67	10	**REFERENCE**	**REFERENCE**
62.1 – 63.9	28	1.07 [0.67 – 1.71]	67.1 – 68.9	28	2.02 [0.95 – 4.27]	1.37 [0.75 – 2.50]

ALL PRIMARY OPEN ANGLE GLAUCOMA:						
Category in inches: NHS	**NHS cohort**		**Category in inches: HPFS**	**HPFS cohort**		**Pooled MVRR†**
	# Cases	**MVRR†**		**# Cases**	**MVRR†**	
64 – 65.9	63	0.98 [0.67 – 1.43]	69 – 70.9	20	2.07 [0.95 – 4.51]	1.31 [0.64 – 2.68]
66 – 66.9	42	1.48 [0.97 – 2.24]	71 – 72.9	19	1.37 [0.62 – 3.02]	1.45 [1.01 – 2.10]
67+	46	1.25 [0.83 – 1.87]	73+	18	2.05 [0.91 – 4.61]	1.41 [0.93 – 2.13]
P for trend		0.10			0.20	0.04
Linear BMI		1.04 [0.98–1.09]; p = 0.20			1.03 [0.94–1.11]; p = 0.56	1.03 [0.99–1.08]; p = 0.16

*Cohort-specific results were pooled using random effects.

†MVRR=Multivariate relative risk adjusted for age (years), family history of glaucoma, African American heritage, smoking (0,1–9, 10–19, 20–29, 30+ pack years), physical activity (quartiles of Met-hours/week), cumulatively updated alcohol intake (0, <5, 5–14, 15–29, 30+ g/d), weight residuals (5 categories).

BMI=body mass index; NHS=Nurses' Health Study; HPFS=Health Professionals Follow-Up Study

Table 5

Cohort specific and pooled analyses of body mass index adjusted cumulatively averaged hip circumference in relation to risk of primary open-angle glaucoma (POAG), high tension POAG (intraocular pressure > 21 mm Hg) and normal tension POAG (intraocular pressure ≤ 21 mm Hg)

ALL PRIMARY OPEN ANGLE GLAUCOMA:						
Category in inches: NHS	**NHS cohort**		**Category in inches: HPFS**	**HPFS cohort**		**Pooled MVRR†**
	# Case	**MVRR†**		**# Cases**	**MVRR†**	
<36.8	96	**REFERENCE**	20.2 – 37.6	63	**REFERENCE**	**REFERENCE**
37 – 38.5	95	0.84 [0.62 – 1.12]	37.9 – 39.3	51	0.87 [0.58 – 1.29]	0.85 [0.67 – 1.08]
38.7 – 40	101	0.98 [0.72 – 1.33]	39.4 – 40.5	61	0.88 [0.59 – 1.31]	0.94 [0.73 – 1.20]
40.3 – 42.8	97	0.89 [0.63 – 1.26]	40.9 – 42.7	62	0.96 [0.63 – 1.48]	0.92 [0.70 – 1.20]
43+	79	0.71 [0.47 – 1.08]	42.8+	53	0.75 [0.45 – 1.23]	0.73 [0.53 – 1.00]
P for trend		0.17			0.39	0.11
Linear hip circumference		1.00 [0.96–1.03]; p = 0.90			1.00 [0.95–1.05]; p = 0.90	1.00 [0.97–1.03]; p = 0.86
POAG WITH INTRAOCULAR PRESSURE > 21 mm Hg AT VISUAL FIELD LOSS:						
Category in inches: NHS	NHS cohort		Category in inches: HPFS	HPFS cohort		Pooled MVRR†
	# Cases	MVRR†		# Cases	MVRR†	
<36.8	58	**REFERENCE**	20.2 – 37.6	50	**REFERENCE**	**REFERENCE**
37 – 38.5	61	0.87 [0.60 – 1.26]	37.9 – 39.3	32	0.62 [0.38 – 1.00]	0.76 [0.55 – 1.06]
38.7 – 40	58	0.93 [0.62 – 1.39]	39.4 – 40.5	47	0.74 [0.47 – 1.17]	0.84 [0.62 – 1.14]
40.3 – 42.8	61	0.91 [0.59 – 1.42]	40.9 – 42.7	42	0.72 [0.44 – 1.18]	0.83 [0.60 – 1.15]
43+	49	0.65 [0.38 – 1.11]	42.8+	36	0.58 [0.32 – 1.03]	0.63 [0.42 – 0.93]
P for trend		0.16			0.15	0.05
Linear BMI		0.99 [0.95–1.04]; p = 0.79			0.97[0.91–1.03]; p = 0.36	0.99[0.95–1.02]; p = 0.46
POAG WITH INTRAOCULAR PRESSURE ≤ 21 mm Hg AT VISUAL FIELD LOSS:						
Category in inches: NHS	NHS cohort		Category in inches: HPFS	HPFS cohort		Pooled MVRR†
	# Cases	MVRR†		# Cases	MVRR†	
<36.8	38	**REFERENCE**	20.2 – 37.6	13	**REFERENCE**	**REFERENCE**
37 – 38.5	34	0.78 [0.48 – 1.25]	37.9 – 39.3	19	1.91 [0.88 – 4.15]	1.15 [0.48 – 2.77]

ALL PRIMARY OPEN ANGLE GLAUCOMA:						
Category in inches: NHS	**NHS cohort**		**Category in inches: HPFS**	**HPFS cohort**		**Pooled MVRR†**
	# Case	**MVRR†**		**# Cases**	**MVRR†**	
38.8 – 40	43	1.05 [0.64 – 1.70]	39.4 – 40.5	14	1.45 [0.62 – 3.43]	1.13 [0.74 – 1.73]
40.3 – 42.8	36	0.86 [0.49 – 1.49]	40.9 – 42.7	20	2.02 [0.84 – 4.83]	1.23 [0.54 – 2.81]
43+	30	0.83 [0.42 – 1.62]	42.8+	17	1.56 [0.57 – 4.27]	1.01 [0.57 – 1.79]
P for trend		0.67			0.47	0.67
Linear BMI		1.00[0.95–1.06]; p = 0.89			1.06[0.97–1.15]; p = 0.23	1.01[0.96–1.07]; p = 0.66

*Cohort-specific results were pooled using random effects.

†MVRR=Multivariate relative risk adjusted for age (years), family history of glaucoma, African American heritage, smoking (0,1–9, 10–19, 20–29, 30+ pack years), physical activity (quartiles of Met-hours/week), cumulatively updated alcohol intake (0, <5, 5–14, 15–29, 30+ g/d), body mass index (6 categories).

BMI=body mass index; NHS=Nurses' Health Study; HPFS=Health Professionals Follow-Up Study