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A prospective study of diabetes, lifestyle factors, and glaucoma in African-American women

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Abstract

PURPOSE—To evaluate the association of self-reported type 2 diabetes, anthropometric factors, alcohol consumption, and cigarette smoking with risk of primary open-angle glaucoma (POAG) in a prospective cohort study of African-American women.

METHODS—From 1995 through 2007, 32,570 Black Women's Health Study participants aged 21–69 at baseline were followed for incident POAG. Questionnaires were mailed biennially to update exposures and identify incident cases of POAG. Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were derived from Cox regression models.

RESULTS—During 416,171 person-years of follow-up, 366 incident POAG cases were confirmed by physician report. After adjustment for potential confounders, the IRR comparing women with and without type 2 diabetes was 1.58 (95% CI=1.17–2.13), and the IRR comparing current with never alcohol consumers was 1.35 (95% CI=1.05–1.73). Among women age <50 years, associations with diabetes and alcohol consumption were stronger, and POAG was significantly associated with BMI, waist circumference, waist-to-hip ratio, and both long-duration and high-intensity current smoking.

CONCLUSIONS—These results suggest that type 2 diabetes and current alcohol consumption are independent risk factors for POAG in African-American women, and that in addition to those factors, overall and central adiposity and smoking may be associated with increased risk of early-onset POAG

MeSH Key words

african-americans; female; diabetes; anthropometry; smoking; alcohol; primary open-angle glaucoma

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BACKGROUND

Glaucoma is the second leading cause of blindness worldwide (1) and affects more than 2 million individuals in the United States (2). The most common form, primary open-angle glaucoma (POAG), is at least 3 times more common among African-Americans than Caucasians (2–4). Reasons for the ethnic disparity in POAG rates remain poorly understood. Risk factors for POAG include older age (5), family history of POAG (6), and ocular hypertension (7–10). Some studies have found an increased risk among men relative to women (5, 6), but others have found a decreased risk (11) or no difference in risk (2, 4).

Type 2 diabetes is a growing problem among African-American women (12). Some studies have found significant (13–15) and non-significant (16) positive associations between type 2 diabetes and POAG risk, while other studies have found no association (17–25), including several studies of participants with African ancestry (17, 19–21, 23, 25). Whether anthropometric factors such as overall adiposity (as measured by body mass index (BMI)) or central adiposity (as measured by waist circumference or waist-to-hip ratio (WHR)) are determinants of POAG risk is unclear. Studies have found both positive (21) and inverse associations (6, 13, 26) between BMI and POAG, and we know of no studies that have evaluated central adiposity. Studies of smoking and POAG risk have yielded both positive (21–23, 27, 28) and null results (29–32), while most studies of alcohol consumption and POAG risk have been null (21–23, 29–31, 33, 34).

The present report evaluates the association of type 2 diabetes, anthropometric factors, alcohol consumption, and cigarette smoking with risk of incident POAG in the Black Women's Health Study (BWHS), a large prospective cohort study of African-American women.

METHODS

Study population

The Black Women's Health Study (BWHS) is an ongoing U.S. prospective cohort study, established in 1995 when 59,000 African-American women aged 21–69 were enrolled through mailed questionnaires (35). The baseline questionnaire elicited information on demographic, lifestyle, and behavioral characteristics, health care utilization, and medical history. The cohort is followed every 2 years by postal questionnaire and cohort retention has exceeded 80% through 2007. The institutional review board of Boston University Medical Center approved the study protocol.

Assessment of POAG

On the 1995, 1997, and 1999 questionnaires, women reported "glaucoma" under an openended question about "other serious illness" along with the year of first diagnosis. On subsequent follow-up questionnaires, women reported whether they had been diagnosed with "glaucoma" by a physician and the year of first diagnosis. Incident cases were those who reported to have been *first* diagnosed after March 1995.

A validation study to confirm self-reported incident glaucoma was initiated in 2005 and is ongoing. Participants are asked for permission to review their medical records regarding the diagnosis of glaucoma. The participant's treating ophthalmologist or optometrist is asked to complete a questionnaire about the diagnosis and/or send copies of ocular records for review by the study ophthalmologists (J.M.S., C.M., E.B.Y.). The questionnaire asks about the diagnosis (primary open angle glaucoma, secondary glaucoma, narrow angle glaucoma, suspect glaucoma, and ocular hypertension), year of first diagnosis, signs of glaucoma, treatment history (date of initiation of medication(s), type and name of medication(s), laser

or other surgery for POAG), family history of POAG, and whether there was gonioscopic evidence of open angles. In primary analyses, confirmed cases of POAG were defined as women whose physicians reported they had "primary open angle glaucoma" (current version of questionnaire) or "glaucoma" (2005 version of questionnaire), *and* at least two of three of the following glaucomatous signs: 1) "visual field defect," 2) "increased intraocular pressure," or 3) "optic nerve findings."

To date, 812 women among the 1,426 who reported incident glaucoma have responded to our request for medical information. Of these, 640 (79%) gave permission to review their medical records, 93 (11%) denied the diagnosis, and 79 (10%) refused. We obtained medical record data for 630 of the 640 women who gave us permission (98%) and confirmed the self-report in 403 (64%). Of the 403 confirmed cases, 369 (92%) had POAG, 14 had secondary glaucoma (3%), 18 had narrow-angle glaucoma (4%), and 2 had low-tension glaucoma (<1%). Medical record data indicated that 97% of cases were using eye drops to treat POAG and 27% had surgery or laser treatments. The median age of cases was 56 years (interquartile range: 49–63 years). Of the 227 disconfirmed cases, most were classified by their physician as "suspect glaucoma" or "ocular hypertension" (90%), 7% had other ocular conditions such as diabetic retinopathy or cataracts, and 3% had no ocular condition. Of the 369 women with confirmed POAG, 3 had missing data on diabetes or BMI, leaving a total of 366 cases for the present analysis. Disconfirmed cases were treated as non-cases for the remainder of follow-up and cases pending validation were censored at their reported year of diagnosis.

Prevalence estimates for overweight and obesity at baseline were lower among women whose eye exam records were reviewed compared with those whose records were not reviewed (BMI \geq 30: 33% versus 42%; BMI \geq 25: 69% versus 76%), but estimates were similar with respect to diabetes (10% versus 14%), current smoking (16% vs. 20%), current drinking (29% vs. 27%), age (mean: 49.3 vs. 48.8 years), WHR (0.80 in both groups), and waist circumference (33.2 vs. 33.5 inches).

Assessment of exposures and covariates

On the 1995 questionnaire, participants reported whether they had ever been diagnosed with "diabetes (not during pregnancy)," their age at first diagnosis: <30, 30-39, 40-49, and ≥ 50 years, whether they were currently taking insulin or pills for diabetes, and the duration of medication use (<1, 1, 2, 3–4, \geq 5 years). On each follow-up questionnaire, women were asked if they had been diagnosed with "diabetes not during pregnancy" in the prior two-year interval, the year of first diagnosis, and the use of injections or pills for diabetes. Women who reported diabetes with an age at first diagnosis before 30 years were excluded from analyses of type 2 diabetes because of the possibility that they had type 1 diabetes (36–38). The accuracy of self-reported diabetes was assessed in a random sample of 656 women who reported a diagnosis after 1995. These women were asked to sign a release for their physician to be contacted, after which we mailed a questionnaire to the treating physician about criteria used for diagnosis (abnormal fasting blood glucose: >126 mg/dl or >140 mg/ dl, casual plasma glucose level >200 mg/dl, oral glucose tolerance test >200 mg/dl, or other), the year of first diagnosis, and medications prescribed. Of the 293 women providing permission to contact their physicians, 229 physicians returned a completed questionnaire and 200 (96%) of these cases were confirmed: 217 had type 2 diabetes, 2 had type 1 diabetes, and 1 had steroid-induced diabetes. Of the 9 disconfirmed cases, 4 had metabolic syndrome, 2 had gestational diabetes, and 3 did not have diabetes.

In 1995, we collected data on self-reported height (in feet and inches), current weight (in pounds), weight at age 18 (in pounds), waist circumference at the level of the umbilicus (in inches), and hip circumference at its widest location (in inches). Current weight was updated

every two years by follow-up questionnaire. BMI was calculated as weight (kg) divided by height squared (m²). Data on cigarette smoking, alcohol consumption, hypertension (and use of diuretics or antihypertensive medications), and physical activity were obtained at baseline and updated on all follow-up questionnaires. Education and energy intake as measured by Food Frequency Questionnaire (39) were ascertained at baseline. In 2001, we conducted a validation study of anthropometric measures among 115 BWHS participants in which Spearman correlations for self-reported versus technician-measured weight, height, waist circumference, and hip circumference were 0.97, 0.93, 0.75, and 0.74, respectively (40).

Exclusion criteria

Of the 59,028 women who completed the 1995 (baseline) questionnaire, we excluded women who did not complete at least one of the 2001, 2003, 2005, and 2007 questionnaires on which we asked specifically about glaucoma (N=5,454); those reporting "glaucoma" without a date of first diagnosis (N=168) or with a date before baseline (N=377); and those with incomplete information on important covariates (N=398). To reduce potential for detection bias, we further excluded non-cases who did not report having an eye exam within the past 2 years on the 2007 questionnaire (N=20,061). After these exclusions, 32,570 women remained in the present analyses. There were no appreciable differences between women who were and were not included in the analysis with respect to the prevalence of diabetes at baseline (3.9% vs. 4.3%), age at baseline (39.5 vs. 38.5 years), and anthropometric measures (BMI \geq 25: 62% in both groups, BMI \geq 30: 30% vs. 31%, mean waist circumference: 32 inches in both groups, mean WHR: 0.79 vs. 0.80). However, those included were less likely than those excluded to report current smoking (14% vs. 19%) and more likely to report alcohol consumption (29% vs. 25%) at baseline.

Data Analysis

Each participant contributed person-time from March 1995 until the diagnosis of POAG, death, loss to follow-up, or end of follow-up (March 2007), whichever came first. Analyses were carried out using SAS statistical software (version 9.1) (41). We used age- and time-stratified Cox regression (42, 43) to estimate incidence rate ratios (IRRs) and 95 percent confidence intervals (CI) for selected exposure variables in relation to risk of incident POAG. BMI was categorized according to WHO standards (44) and the other lifestyle variables were categorized based on their frequency distributions among non-cases. In multivariable Cox models, we mutually adjusted for each exposure variable. For example, in the assessment of BMI, terms were included for alcohol consumption (<1, 1–6, \geq 7 drinks/ week), cigarette smoking (current, past, never), and diabetes (no, yes without medications, yes with pills, yes with injections). We adjusted for adult BMI in analyses of each anthropometric variable except for weight change since age 18.

Potential POAG risk factors that were associated with the exposures of interest at baseline (Table 1) were added to the multivariable model, including education (≤ 12 , 13–16, ≥ 17 years), hypertension (no, yes without medications, yes with medications), vigorous physical activity (none, <5, ≥ 5 hours/week), and energy intake (<1000, 1,000–1,499, $\geq 1,500$ kilocalories/day). To test for trend, we modeled a single ordinal term coded as the score of each exposure category (including the unexposed) (45). Departures from the proportional hazards assumption were tested by the likelihood ratio test comparing models with and without cross-product terms for each exposure with age (<50 versus ≥ 50) and time period.

RESULTS

Among the 32,570 participants in the present analysis, 3% reported having type 2 diabetes, 32% were overweight (BMI 25–29 kg/m²), and 30% were obese (BMI \ge 30 kg/m²) in 1995

(Table 1). Type 2 diabetes was positively associated with age, BMI, waist circumference, WHR, adult weight gain, energy intake, hypertension, and smoking, and inversely associated with education, alcohol consumption, and vigorous exercise. Obesity (BMI \geq 30 kg/m²) was positively associated with age, adult weight gain, energy intake, diabetes, and hypertension, and inversely associated with height, education, and vigorous exercise. WHR was positively associated with BMI, adult weight gain, energy intake, hypertension, and diabetes. Current drinking was positively associated with age, current drinking, energy intake, and hypertension, and inversely associated with age, current drinking, energy intake, and hypertension, and inversely associated with education and adult weight gain.

There were 366 incident cases of POAG confirmed by physician report during 416,171 person-years of follow-up. Type 2 diabetes was positively associated with POAG risk (Table 2). The multivariable incidence rate ratio (IRR) comparing women with and without type 2 diabetes was 1.58 (95% CI: 1.17–2.13). Type 2 diabetes treated with pills or injections was associated with increased POAG risk, but untreated diabetes was not. There was no evidence that POAG risk increased with increasing years since diabetes diagnosis (*P*-trend=0.64).

BMI, weight gain since age 18, height, waist circumference, and WHR were not associated with POAG risk in multivariable models (Table 2). Further control for BMI at age 18 had little effect on the IRR for weight gain since age 18 (data not shown). Current alcohol consumption was positively associated with POAG risk: the multivariable IRR was 1.35 (95% CI: 1.05–1.73) for current drinking relative to never drinking, and 1.60 (95% CI: 1.06–2.43) for current consumption of \geq 7 drinks/week relative to non-drinking. Cigarette smoking, whether defined by recency, intensity, or duration of smoking, was not associated with POAG risk. While some associations observed in the overall sample were stronger among younger (age <50) than older women (age \geq 50), significant age-interactions were found only for BMI and waist circumference (Table 3).

In analyses that excluded cases with "increased intraocular pressure" as a glaucomatous sign, the association between diabetes and POAG was stronger than that found in the original analysis (N=329 cases: IRR=1.69, 95% CI: 1.24–2.30), suggesting that bias due to greater detection among diabetics with increased intraocular pressure did not explain our results. In analyses restricted to cases for whom "visual field defect" was noted as a glaucomatous sign (N=215 cases), the multivariable IRR comparing women with and without type 2 diabetes was 1.47 (95% CI: 0.99–2.18) and the IRR for current relative to never alcohol consumption was 1.32 (95% CI: 0.95–1.83). Suggestive positive associations were also found among non-cases with "suspect glaucoma" or "ocular hypertension" (N=203) in association with type 2 diabetes (IRR=1.42, 95% CI: 0.94–2.13) and current alcohol consumption of \geq 7 drinks per week (IRR=1.61, 95% CI: 0.95–2.74). Finally, in analyses that added back the women who did not report a recent eye exam (N=20,061), associations of POAG with BMI and diabetes were similar to those presented in the primary analyses (data not shown).

DISCUSSION

In the present study of over 32,000 African-American women aged 21–69 years, type 2 diabetes was associated with a 58% increased risk of POAG overall, and a more than two-fold increased risk of POAG among women under age 50 years. Current alcohol consumption was also positively associated with POAG. Overall and central adiposity and smoking were associated with increased risk of early-onset POAG, albeit the smoking findings were based on small numbers of heavy smokers.

Our overall results for type 2 diabetes are consistent with two cohort studies among Caucasians that reported relative risks in the range of 1.6 to 1.8 (13, 16), and a meta-analysis of case-control and cross-sectional studies that reported a 1.5-fold increased risk (14). However, our findings conflict with other cross-sectional (18–20), case-control (21–23), and prospective (17, 24, 25, 28) studies showing no association, including several studies that enrolled large numbers of participants with African ancestry (17, 19–21, 25).

Diabetes may influence risk of POAG via hyperglycemia-related vascular constriction leading to elevated intraocular pressure (46, 47) and increased susceptibility to glaucomatous optic nerve damage (48). According to Sato and Roy, high glucose levels in the aqueous humor of patients with diabetes may increase fibronectin synthesis and accumulation in the trabecular meshwork (49). The accelerated depletion of trabecular meshwork cells is a characteristic feature of the outflow system in POAG (49). Pasquale et al. noted the correlation between glycosylated hemoglobin and increased ocular pressure (13, 50, 51) and speculated that glycosylation of extracellular matrix proteins in the trabecular meshwork could further reduce outflow facility in patients with type 2 diabetes (13). Therefore, relative obstruction of the outflow of aqueous humor via the trabecular meshwork may be a primary mechanism by which diabetes affects POAG risk. To our knowledge, there are no studies that have assessed blood glucose levels or level of glycemic control among diabetics in relation to POAG risk, but such studies would permit a direct test of this hypothesis.

With regard to anthropometric factors, one case-control study among African Blacks found a weak positive association between BMI and POAG after control for diabetes (21), while three other studies in Black (6) and White (13, 26) populations found an inverse association. None of these studies stratified by age. Most studies of alcohol consumption and POAG risk have been case-control studies. They have largely reported null associations (21, 22, 30, 31, 52) except for a small study that reported a strong inverse association (27). One case-control study of ocular hypertension also suggested an inverse association (8). The only prospective study is the pooled analysis of the Nurses' Health Study and the Health Professionals Follow-up Study, in which results were null for current drinkers having the same level of exposure as our study (53).

Previous results on cigarette smoking come largely from case-control studies, yielding positive (21–23, 27, 28) and null (29–31, 33) associations. A pooled analysis of two prospective cohort studies, the Nurses Health Study and the Health Professionals Follow-up Study, found no overall association between current smoking and POAG (32). Similar to the present investigation, those studies were prospective, confined to participants with recent eye exams and to cases confirmed by medical record, and controlled for several risk factors for POAG. However, these studies did not stratify by age.

To our knowledge, only one study has examined whether risk factors for early-onset POAG differ from late onset POAG (54). The Baltimore Eye study found a positive association between systemic hypertension and POAG overall, but the association was stronger in older than younger participants (54). It is plausible, as observed in the present study, that some risk factors are stronger for early-onset illness than for later-onset disease. For example, heavy cigarette smoking is associated with a doubling or less in risk of myocardial infarction among elderly men and women, but the relative increase in risk of myocardial infarction for heavy smokers less than 45 years of age is at least tenfold (55–58).

A study limitation is that participants were not systematically screened for POAG. To minimize the potential for underdetection of POAG, we confined the analytic sample to women who reported a recent eye examination. However, if women with diabetes were

more likely to receive a comprehensive eye examination for POAG relative to those without diabetes, a spurious positive association between diabetes and POAG would have resulted. We believe that such diagnostic bias is unlikely in the present study for two reasons: 1) the findings for time since diagnosis of diabetes did not reveal a peak in POAG risk shortly after diagnosis with diabetes, but rather a similar increased magnitude in POAG risk over time, and 2) there was no increased risk of POAG among other groups for which a more comprehensive eye exam was also likely (e.g., hypertensives). Nonetheless, we cannot rule out the possibility that a more comprehensive eye exam among diabetics contributed to the positive associations observed in this study.

All cases were confirmed by physician diagnosis to maximize specificity. Because we relied on the judgment of the diagnosing eye care provider that glaucomatous optic neuropathy was present, and because different ophthalmologists will not have used exactly the same criteria, some cases may have been misclassified. However, the findings from secondary analyses implementing more stringent case definitions were highly consistent with the overall findings.

Our study had several strengths. The BWHS is the largest study to date of POAG in African-American women, a group at increased risk of POAG (2, 3, 11). Accuracy of self-reported type 2 diabetes, weight, height, waist circumference and hip circumference has been shown in validation studies. The prospective assessment of risk factors for POAG served both to clarify the temporal relationship of the associations examined and to minimize reporting bias. We controlled for several POAG risk factors in multivariable models, thereby reducing the potential for confounding. Although the BWHS is a convenience sample of African-American women with higher levels of education than the general population, associations identified in our study did not vary appreciably by factors other than age. Moreover, rates of POAG were similar to those found in other studies of black women (59), suggesting our results may extend to a wider population of black women. Finally, high cohort retention (>80%) reduced the likelihood of selection bias.

At present, few modifiable risk factors for POAG have been identified. Observations from the present study regarding the association of type 2 diabetes with POAG are consistent with several studies conducted to date. In addition, many of these findings are new for African-American women. Confirmation of these associations in a population systematically screened for POAG would be desirable. Since the prevalence of type 2 diabetes is 2- to 3-fold higher in African-American women than Caucasian women (12), efforts to reduce the occurrence of type 2 diabetes could have a large impact on POAG incidence in this population. In addition, if confirmed, the positive associations of POAG with alcohol consumption, as well as with obesity and cigarette smoking in younger women, provide an opportunity for primary prevention efforts.

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List of abbreviations and acronyms

BMI	body mass index
WHR	waist-to-hip ratio

POAG	primary open angle glaucoma
IRR	incidence rate ratio
CI	confidence interval

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Table 1

Baseline characteristics of 32,570 women according to type 2 diabetes, body mass index, waist to hip ratio, and drinking and smoking status in the Black Women's Health Study, 1995*

	Type 2]	Diabetes	Body mass in	dex (kg/m ²)	Waist-to-	hip ratio †	Alcohol	intake	Cigarette	smoking
Characteristic	Yes	No	<25	≥30	<0.72	≥0.85	Current	Never	Current	Never
No. of women	1,055	31,294	12,406	9,698	6,788	6,654	9,069	18,713	4,634	21,471
Age, yrs (mean)	50.3	39.1	36.8	41.2	39.0	39.2	40.6	38.2	41.2	37.5
Education, yrs (mean)	14.4	14.9	15.1	14.6	15.1	14.5	14.8	15.0	14.2	15.0
BMI, kg/m ² (mean)	34.2	27.8	22.4	36.0	26.1	29.8	27.7	27.8	27.8	27.8
BMI at age 18, kg/m ² (mean) $\mathring{\tau}$	23.6	21.3	19.4	24.5	21.0	21.8	21.3	21.3	21.7	21.2
Height, inches (mean)	65.0	65.0	65.2	64.8	65.0	65.0	65.1	65.0	65.1	64.9
Waist circumference, inches (mean) \S	36.5	32.0	28.3	37.3	28.1	36.3	32.0	32.0	32.2	31.9
Waist-to-hip ratio (mean) $\dot{\tau}$	0.82	0.79	0.76	0.82	0.7	0.9	0.8	0.8	0.8	0.8
Weight gain since age 18, kg (mean) \ddagger	28.9	17.7	8.1	31.2	13.9	21.8	17.3	17.8	16.6	18.0
Alcohol intake, drinks/wk (mean)	0.83	1.4	1.4	1.3	1.2	1.6	5.4	0	3.1	0.8
Cigarette smoking, packyrs (mean)	5.0	3.9	3.5	4.2	3.3	4.6	6.0	2.3	12.4	0
Vigorous exercise, hrs/wk (mean)	1.4	2.0	2.4	1.4	2.4	1.7	2.2	1.9	1.8	2.0
Energy intake, kcal/dy (mean)	1,743	1,639	1,509	1,859	1554	1767	1739	1580	1759	1604
History of type 2 diabetes (%)	1	I	1.2	5.8	1.8	5.3	2.1	3.2	3.2	3.1
History of treated hypertension (%)	41.9	13.4	7.8	22.0	10.6	18.8	14.1	14.2	15.2	14.4
* Characteristics (with exception of age) a	re standar	dized to ag	e distribution o	of women at ba	seline.					
$^\dagger\mathrm{Based}$ on 27,560 women with complete	informatic	on on waist	and hip circum	ıference.						

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 t^{\dagger} Based on 32,305 women with complete information on weight at age 18. \$ Based on 28,238 women with complete information on waist circumference.

Table 2

Association of diabetes, anthropometric factors, alcohol consumption, and cigarette smoking with risk of primary open-angle glaucoma. The Black Women's Health Study, 1995–2007.

Characteristic	Cases	Person-years	Model 1 IRR (95%CI)*	Model 2 IRR (95%CI) [†]
All women	366	416,171		,
Type 2 diabetes				
No	308	389,470	1.00‡	1.00‡
Yes	57	23,488	1.48 (1.11, 1.98)	1.58 (1.17, 2.13)
Type of treatment:				
None	9	6,166	1.00 (0.52, 1.96)	1.05 (0.54, 2.05)
Pills	36	12,828	1.69 (1.19, 2.40)	1.82 (1.26, 2.61)
Injections	12	4,494	1.48 (0.82, 2.64)	1.59 (0.88, 2.86)
Years since diagnosis:				
< 5	25	9,934	1.73 (1.15, 2.62)	1.84 (1.21, 2.81)
5–9	13	7,134	1.24 (0.71, 2.17)	1.33 (0.76, 2.35)
10-14	8	3,581	1.23 (0.61, 2.52)	1.32 (0.64, 2.70)
≥ 15	11	2,839	1.55 (0.84, 2.88)	1.64 (0.88, 3.05)
Test for ordinal trend			<i>p</i> =0.71	<i>p</i> =0.64
Body mass index, kg/m ²				
< 25	89	126,458	1.00≠	1.00⊄
25–29	130	138,500	0.94 (0.72, 1.24)	0.95 (0.72, 1.24)
30–34	74	81,546	0.86 (0.63, 1.18)	0.86 (0.63, 1.18)
≥ 35	73	69,667	1.14 (0.83, 1.55)	1.14 (0.82, 1.59)
Test for ordinal trend			<i>p</i> =0.73	<i>p</i> =0.76
Weight change since age 18	, kg [§]			
< 10	56	93,985	1.00^{\ddagger}	1.00≠
10–14	43	63,942	0.82 (0.55, 1.22)	0.82 (0.55, 1.21)
15–24	120	120,634	0.98 (0.71, 1.35)	0.98 (0.71, 1.35)
≥ 25	142	134,304	0.92 (0.67, 1.26)	0.92 (0.67, 1.27)
Test for ordinal trend			<i>p</i> =0.69	<i>p</i> =0.69
Height, feet and inches				
< 5'3"	89	78,497	1.00≠	1.00⊄
5'3" - 5'4"	86	106,807	0.75 (0.56, 1.01)	0.74 (0.55, 0.99)
5′5″ - 5′6″	107	113,704	0.91 (0.68, 1.20)	0.89 (0.67, 1.18)
≥ 5′7″	84	117,163	0.80 (0.59, 1.07)	0.77 (0.57, 1.04)
Test for ordinal trend			<i>p</i> =0.34	<i>p</i> =0.26
Waist circumference, inches	1			
< 29	63	103,383	1.00	1.00 [‡]
29–31	66	74,303	1.34 (0.91, 1.97)	1.38 (0.93, 2.06)
32–34	92	94,024	1.18 (0.80, 1.74)	1.24 (0.81, 1.90)
≥ 35	94	89,103	1.30 (0.88, 1.91)	1.28 (0.81, 2.04)

Test for ordinal trend $p=0.60$ $p=0.81$ Waist-to-hip ratio [#] 1.00 [‡] 1.00 [‡] 0.72 62 86.995 1.00 [‡] 1.00 [‡] 0.72-0.77 97 95,171 1.27 (0.92, 1.75) 1.26 (0.92, 1.74) 0.78-0.84 66 85,234 0.98 (0.69, 1.38) 0.98 (0.69, 1.39) ≥ 0.85 84 84,769 1.34 (0.96, 1.86) 1.35 (0.96, 1.89) Test for ordinal trend $p=0.26$ $p=0.26$ $p=0.26$ Alcohol consumption Never 145 197,425 1.00 [‡] 1.00 [‡] Former 90 92,997 1.01 (0.78, 1.32) 1.03 (0.78, 1.36) Current Current labohol consumption None 235 290,422 1.00 [‡] 1.00 [‡] None 235 290,422 1.00 [‡] 1.00 [‡] 1.00 [‡] 1-6 drinks per week 105 106,057 1.24 (0.98, 1.56) 1.28 (1.01, 1.62) ≥ 7 drinks per week 105 106,057 1.24 (0.98, 1.51) 1.16 (0.36, 1.55)	Characteristic	Cases	Person-years	Model 1 IRR (95%CI)*	Model 2 IRR $(95\%$ CI) [†]	
Waist-to-hip ratio [#] <0.72 62 86.995 1.00^{1} 1.00^{1} 1.26 (0.92, 1.74) 0.72-0.77 97 95,171 1.27 (0.92, 1.75) 1.26 (0.92, 1.74) 0.78-0.84 66 85,234 0.98 (0.69, 1.38) 0.98 (0.69, 1.39) ≥ 0.85 84 84,769 1.44 (0.96, 1.86) 1.35 (0.96, 1.89) <i>Test for ordinal trend</i> $P = 0.26$ $P = 0.16$ $P = 0.26$ $P = 0.17$ Current alcohol consumption $P = 0.26$ $P = 0.17$ Years of alcohol consumption $P = 0.26$ $P = 0.17$ $P = 0.26$ $P = 0.26$	Test for ordinal trend			<i>p</i> =0.60	<i>p</i> =0.81	
< 0.72	Waist-to-hip ratio [#]					
0.72-0.77 97 95,171 1.27 (0.92, 1.75) 1.26 (0.92, 1.74) 0.78-0.84 66 85,234 0.98 (0.69, 1.38) 0.98 (0.69, 1.39) ≥ 0.85 84 84,769 1.34 (0.96, 1.86) 1.35 (0.96, 1.89) Test for ordinal trend $p=0.26$ $p=0.26$ Alcohol consumption $p=0.26$ $p=0.26$ Never 145 197,425 1.00° 1.00° Former 90 92,997 1.01 (0.78, 1.32) 1.03 (0.78, 1.36) Current alcohol consumption 131 125,129 1.20° 1.00° I-6 drinks per week 26 19,072 1.52 (101, 2.28) 1.60 (1.06, 2.43) <i>T crinks per week</i> 26 19,072 1.52 (1.01, 2.28) 1.60 (1.06, 2.43) <i>T crinks per week</i> 26 19,072 1.52 (1.01, 2.28) 1.60 (1.06, 2.43) <i>T crinks per week</i> 26 19,072 1.52 (1.01, 2.28) 1.00° 1-9 69 96,137 1.13 (0.84, 1.51) 1.16 (0.86, 1.55) 10-19 42 52,404 1.18 (0.83, 1.66) 1.23 (0.86, 1.76) <	< 0.72	62	86,995	1.00‡	1.00^{\ddagger}	
0.78-0.84 66 85,234 0.98 (0.69, 1.38) 0.98 (0.69, 1.38) ≥ 0.85 84 84,769 1.34 (0.96, 1.86) 1.35 (0.96, 1.89) Test for ordinal trend $p=0.26$ $p=0.26$ Alcohol consumption 1.00 ⁷ 1.00 ⁷ Never 145 197,425 1.00 ⁷ 1.03 (0.78, 1.36) Current 131 125,129 1.29 (1.02, 1.63) 1.35 (1.05, 1.73) Current alcohol consumption	0.72-0.77	97	95,171	1.27 (0.92, 1.75)	1.26 (0.92, 1.74)	
≥ 0.85 84 84,769 1.34 (0.96, 1.80) 1.35 (0.96, 1.89) Test for ordinal trend $p=0.26$ $p=0.26$ Alcohol consumption $p=0.26$ $p=0.26$ Never 145 197,425 1.00° 1.00° Former 90 92,997 1.01 (0.78, 1.32) 1.03 (0.78, 1.36) Current alcohol consumption 235 290,422 1.00° 1.00° None 235 290,422 1.00° 1.00° 1-6 drinks per week 26 19,072 1.52 (1.01, 2.28) 1.60 (1.06, 2.43) Test for ordinal trend $p=0.26$ $p=0.17$ Years of alcohol consumption $p=0.26$ $p=0.17$ Years of alcohol consumption $p=0.26$ $p=0.17$ Years of alcohol consumption $p=0.86$ $p=0.07$ Years of alcohol consumption $p=0.86$ $p=0.90$ Cigarette smoking $p=0.89$ $p=0.48$ $p=0.90$ Cigarette smoking $p=0.89$ $p=0.48$ $p=0.90$ Current 1.16 <td>0.78–0.84</td> <td>66</td> <td>85,234</td> <td>0.98 (0.69, 1.38)</td> <td>0.98 (0.69, 1.39)</td>	0.78–0.84	66	85,234	0.98 (0.69, 1.38)	0.98 (0.69, 1.39)	
Peolog Peolog Peolog Alcohol consumption Never 145 197,425 1.00^2 1.00^2 1.00^2 Former 90 92,997 $1.01\ 0.78, 1.32$ $1.30\ 0.78, 1.36$ Current 131 125,129 $1.29\ (1.02, 1.63)$ $1.35\ (1.05, 1.73)$ Current alcohol consumption V 1.00^2 1.00^2 1.00^2 None 235 290,422 1.00^2 1.00^2 1.00^2 1 - 6 drinks per week 26 19.072 $1.52\ (1.01, 2.28)$ $1.60\ (1.06, 2.43)$ Test for ordinal trend $p=0.26$ $p=0.17$ $p=0.26$ $p=0.17$ Years of alcohol consumption $p=0.26$ $p=0.17$ 1.00^2 Io=19 42 $52,044$ $1.13\ (0.84, 1.51)$ $1.16\ (0.86, 1.55)$ Io=19 42 $52,929$ 1.00^2 1.00^2 1.00	≥ 0.85	84	84,769	1.34 (0.96, 1.86)	1.35 (0.96, 1.89)	
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Current alcohol consumption 235 290,422 1.00^{f} 1.00^{f} 1-6 drinks per week 105 106,057 1.24 (0.98, 1.56) 1.28 (1.01, 1.62) ≥ 7 drinks per week 26 19,072 1.52 (1.01, 2.28) 1.60 (1.06, 2.43) Test for ordinal trend $p=0.26$ $p=0.17$ Years of alcohol consumption $p=0.26$ $p=0.17$ Years of alcohol consumption 145 197,425 1.00^{f} 1.00^{f} 1-9 69 96,137 1.13 (0.84, 1.51) 1.16 (0.86, 1.55) 10-19 42 52,404 1.18 (0.83, 1.66) 1.23 (0.86, 1.76) ≥ 20 95 59,648 1.11 (0.85, 1.44) 1.15 (0.87, 1.53) <i>Test for ordinal trend</i> $p=0.88$ $p=0.90$ Cigarette smoking 116 81,843 0.95 (0.75, 1.20) 0.89 (0.70, 1.13) Current 116 81,843 0.95 (0.75, 1.20) 0.89 (0.70, 1.13) Current 19 58,929 1.00 (0.7, 1.42) 0.97 (0.70, 1.35) Intensity of smoking** Intensity of smoking** Intensity of smoking** Intensity of smoking** Intensity of	Current	131	125,129	1.29 (1.02, 1.63)	1.35 (1.05, 1.73)	
None 235 290,422 1.00^{f} 1.00^{f} 1-6 drinks per week 105 106,057 1.24 (0.98, 1.56) 1.28 (1.01, 1.62) 2 7 drinks per week 26 19,072 1.52 (1.01, 2.28) 1.60 (1.06, 2.43) Test for ordinal trend $p=0.26$ $p=0.17$ Years of alcohol consumption $p=0.26$ $p=0.17$ Years of alcohol consumption 145 197,425 1.00^{f} 1.00^{f} 1-9 69 96,137 1.13 (0.84, 1.51) 1.16 (0.86, 1.55) 10-19 42 52,404 1.18 (0.83, 1.66) 123 (0.86, 1.76) ≥ 20 95 59,648 1.11 (0.85, 1.44) 1.15 (0.87, 1.53) Test for ordinal trend $p=0.88$ $p=0.90$ Cigarette smoking Never 201 272,257 1.00^{f} 1.00^{f} Former 116 81,843 0.95 (0.75, 1.20) 0.89 (0.70, 1.13) Current 1.94 28,100 0.95 (0.67, 1.33) 0.88 (0.63, 1.25) Current 201 272,257	Current alcohol consumption	on				
1-6 drinks per week 105 106,057 1.24 (0.98, 1.56) 1.28 (1.01, 1.62) ≥ 7 drinks per week 26 19,072 1.52 (1.01, 2.28) 1.60 (1.06, 2.43) Test for ordinal trend $p=0.26$ $p=0.17$ Years of alcohol consumption 1.00 [‡] 1.00 [‡] 1.00 [‡] Years of alcohol consumption 445 197,425 $1.00^{‡}$ 1.00 [‡] 1-9 69 96,137 1.13 (0.84, 1.51) 1.16 (0.86, 1.55) 10-19 42 52,404 1.18 (0.83, 1.66) 1.23 (0.86, 1.76) ≥ 20 95 59,648 1.11 (0.85, 1.44) 1.15 (0.87, 1.53) Test for ordinal trend $p=0.88$ $p=0.90$ Cigarette smoking 1.00 [‡] 1.00 [‡] 1.00 [‡] Former 116 81,843 0.95 (0.75, 1.20) 0.89 (0.70, 1.13) Current 49 58,929 1.04 (0.76, 1.42) 0.97 (0.70, 1.35) Intensity of smoking ^{***} Never 201 272,257 $1.00^{‡}$ 1.00 [‡] Former: 1-14 cigs/day 73 60,559 0.96 (0.74, 1.26) 0.91 (0.69, 1.20) 0.83 (0.56, 1.23)	None	235	290,422	1.00‡	1.00≠	
≥ 7 drinks per week 26 19,072 1.52 (1.01, 2.28) 1.60 (1.06, 2.43) Test for ordinal trend $p=0.26$ $p=0.17$ Years of alcohol consumption Never 145 197,425 1.00^{\ddagger} 1.00^{\ddagger} 1–9 69 96,137 1.13 (0.84, 1.51) 1.16 (0.86, 1.55) 10–19 42 52,404 1.18 (0.83, 1.66) 1.23 (0.86, 1.76) ≥ 20 95 59,648 1.11 (0.85, 1.44) 1.15 (0.87, 1.53) Test for ordinal trend $p=0.88$ $p=0.90$ Cigarette smoking Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Former 116 81,843 0.95 (0.75, 1.20) 0.89 (0.70, 1.13) Current 49 58,929 1.04 (0.76, 1.42) 0.97 (0.70, 1.35) Intensity of smoking ^{***} Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Former; 1–14 cigs/day 73 60,559 0.96 (0.74, 1.26) 0.91 (0.69, 1.20) Former: ≥ 15 cigs/day 41 28,100 0.95 (0.67, 1.33) 0.88 (0.63, 1.25) Current: 1–14 cigs/day 30 39,848 0.88 (0.60, 1.29) 0.83 (0.56, 1.23) Current: ≥ 15 cigs/day 19 12,957 1.45 (0.90, 2.33) 1.35 (0.83, 2.19) Pack-years of smoking ^{***} Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Solution (1.20) 0.83 (0.55, 1.23) Current: 1–14 cigs/day 30 39,848 0.88 (0.60, 1.29) 0.83 (0.56, 1.23) Current: 215 cigs/day 19 12,957 1.45 (0.90, 2.33) 1.35 (0.83, 2.19) Pack-years of smoking ^{***} Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Solution (1.20) 0.72 (0.44, 1.16) 15–19 22 13,715 0.99 (0.63, 1.55) 0.93 (0.59, 1.46) ≥ 20 55 28,888 1.16 (0.85, 1.57) 1.08 (0.79, 1.47) Test for ordinal trend $p=0.33$ $p=0.32$	1-6 drinks per week	105	106,057	1.24 (0.98, 1.56)	1.28 (1.01, 1.62)	
Test for ordinal trend $p=0.26$ $p=0.17$ Years of alcohol consumption Never 145 197,425 1.00^{\ddagger} 1.00^{\ddagger} 1-9 69 96,137 1.13 (0.84, 1.51) 1.16 (0.86, 1.55) 10-19 42 52,404 1.18 (0.83, 1.66) 1.23 (0.86, 1.76) ≥ 20 95 59,648 1.11 (0.85, 1.44) 1.15 (0.87, 1.53) <i>Test for ordinal trend</i> $p=0.88$ $p=0.90$ Cigarette smoking $p=0.90$ 1.00 ‡ 1.00 ‡ Never 201 272,257 1.00^{\ddagger} 1.00 ‡ Former 116 81,843 0.95 (0.75, 1.20) 0.89 (0.70, 1.13) Current 49 58,929 1.04 (0.76, 1.42) 0.97 (0.70, 1.35) Intensity of smoking ** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Former: 1-14 cigs/day 73 60,559 0.96 (0.74, 1.26) 0.91 (0.69, 1.20) Former: 2-15 cigs/day 41 28,100 0.95 (0.67, 1.33) 0.88 (0.63, 1.25) Current: 2-14 cigs/day 30 39,848 0.88 (0.60, 1.29) 0.83 (0.56, 1.23) <td>≥ 7 drinks per week</td> <td>26</td> <td>19,072</td> <td>1.52 (1.01, 2.28)</td> <td>1.60 (1.06, 2.43)</td>	≥ 7 drinks per week	26	19,072	1.52 (1.01, 2.28)	1.60 (1.06, 2.43)	
Years of alcohol consumption Never 145 197,425 1.00^{\ddagger} 1.00^{\ddagger} 1–9 69 96,137 1.13 (0.84, 1.51) 1.16 (0.86, 1.55) 10–19 42 52,404 1.18 (0.83, 1.66) 1.23 (0.86, 1.76) ≥ 20 95 59,648 1.11 (0.85, 1.44) 1.15 (0.87, 1.53) <i>Test for ordinal trend</i> $p=0.88$ $p=0.90$ Cigarette smoking $p=0.90$ 1.00 ‡ 1.00^{\ddagger} Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Former 116 81,843 0.95 (0.75, 1.20) 0.89 (0.70, 1.13) Current 49 58,929 1.04 (0.76, 1.42) 0.97 (0.70, 1.35) Intensity of smoking** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Former: 1-14 cigs/day 73 60,559 0.96 (0.74, 1.26) 0.91 (0.69, 1.20) Former: 2 15 cigs/day 41 28,100 0.95 (0.67, 1.33) 0.88 (0.63, 1.25) Current: 1-14 cigs/day 30 39,848 0.88 (0.60, 1.29) 0.83 (0.56, 1.23) Current: 2 15 cigs/day 19 12	Test for ordinal trend			<i>p</i> =0.26	<i>p</i> =0.17	
Never 145 197,425 1.00^{1} 1.00^{1} 1-9 69 96,137 1.13 (0.84, 1.51) 1.16 (0.86, 1.55) 10-19 42 52,404 1.18 (0.83, 1.66) 1.23 (0.86, 1.76) ≥ 20 95 59,648 1.11 (0.85, 1.44) 1.15 (0.87, 1.53) <i>Test for ordinal trend</i> $p=0.88$ $p=0.90$ Cigarette smoking $p=0.88$ $p=0.90$ Current 201 272,257 1.00^{1} 1.00^{2} Former 116 81,843 0.95 (0.75, 1.20) 0.89 (0.70, 1.13) Current 49 58,929 1.04 (0.76, 1.42) 0.97 (0.70, 1.35) Intensity of smoking** V V V V V Never 201 272,257 1.00^{1} 1.00^{2} Former: 1-14 cigs/day 73 60,559 0.96 (0.74, 1.26) 0.91 (0.69, 1.20) Former: 2 1.5 cigs/day 41 28,100 0.95 (0.67, 1.33) 0.88 (0.63, 1.25) Current: 1-14 cigs/day 30 39,848 0.88 (0.60, 1.29) 0.83 (0.56, 1.23) Current: 2 15 cigs/day	Years of alcohol consumption	ion				
$1-9$ 69 $96,137$ 1.13 ($0.84, 1.51$) 1.16 ($0.86, 1.55$) $10-19$ 42 $52,404$ 1.18 ($0.83, 1.66$) 1.23 ($0.86, 1.76$) ≥ 20 95 $59,648$ 1.11 ($0.85, 1.44$) 1.15 ($0.87, 1.53$) <i>Test for ordinal trend</i> $p=0.88$ $p=0.90$ Cigarette smoking $p=0.88$ $p=0.90$ Cigarette smoking 1.00^{t} 1.00^{t} Former 201 $272,257$ 1.00^{t} 1.00^{t} Former 116 $81,843$ 0.95 ($0.75, 1.20$) 0.89 ($0.70, 1.13$)Current 49 $58,929$ 1.04 ($0.76, 1.42$) 0.97 ($0.70, 1.35$)Intensity of smoking** $Never$ 201 $272,257$ 1.00^{t} 1.00^{t} Former: $1-14$ cigs/day 73 $60,559$ 0.96 ($0.74, 1.26$) 0.91 ($0.69, 1.20$)Former: $1-14$ cigs/day 73 $60,559$ 0.96 ($0.74, 1.26$) 0.91 ($0.69, 1.20$)Former: $1-14$ cigs/day 73 $60,559$ 0.96 ($0.74, 1.26$) 0.91 ($0.69, 1.20$)Current: $1-14$ cigs/day 30 $39,848$ 0.88 ($0.60, 1.29$) 0.83 ($0.56, 1.23$)Current: 215 cigs/day 19 $12,957$ 1.00^{t} 1.00^{t} <10 65 $80,139$ 0.99 ($0.75, 1.31$) 0.94 ($0.71, 1.25$) $10-14$ 18 $21,172$ 0.76 ($0.47, 1.23$) 0.72 ($0.44, 1.16$) $15-19$ 22 $13,715$ 0.99 ($0.63, 1.55$) 0.93 ($0.59, 1.47$) \geq	Never	145	197,425	1.00≠	1.00‡	
$10-19$ 4252,4041.18 (0.83, 1.66)1.23 (0.86, 1.76)≥ 209559,6481.11 (0.85, 1.44)1.15 (0.87, 1.53)Test for ordinal trend $p=0.88$ $p=0.90$ Cigarette smoking $p=0.90$ Never201272,257 1.00^{\ddagger} Former11681,8430.95 (0.75, 1.20)0.89 (0.70, 1.13)Current4958,9291.04 (0.76, 1.42)0.97 (0.70, 1.35)Intensity of smoking** $p=0.90$ 272,257 1.00^{\ddagger} 1.00^{\ddagger} Never201272,257 1.00^{\ddagger} $0.97 (0.70, 1.35)$ Intensity of smoking** $p=0.90$ $0.95 (0.75, 1.20)$ 0.89 (0.70, 1.13)Current:1-14 cigs/day7360,5590.96 (0.74, 1.26)0.91 (0.69, 1.20)Former:1-14 cigs/day7360,5590.96 (0.74, 1.26)0.91 (0.69, 1.20)Former:1-14 cigs/day3039,8480.88 (0.60, 1.29)0.83 (0.56, 1.23)Current:1-14 cigs/day1912,9571.45 (0.90, 2.33)1.35 (0.83, 2.19)Pack-years of smoking** $p=0.272$ 1.00 ‡ 1.00 ‡ Never201272,2571.00 ‡ 1.00 ‡ 106580,1390.99 (0.75, 1.31)0.94 (0.71, 1.25)10-141821,1720.76 (0.47, 1.23)0.72 (0.44, 1.16)15-192213,7150.99 (0.63, 1.55)0.93 (0.59, 1.46)≥ 205528,8881.16 (0.85, 1.57)1.08 (0.79, 1.47) <td cobser<="" td=""><td>1–9</td><td>69</td><td>96,137</td><td>1.13 (0.84, 1.51)</td><td>1.16 (0.86, 1.55)</td></td>	<td>1–9</td> <td>69</td> <td>96,137</td> <td>1.13 (0.84, 1.51)</td> <td>1.16 (0.86, 1.55)</td>	1–9	69	96,137	1.13 (0.84, 1.51)	1.16 (0.86, 1.55)
$ ≥ 20 95 59,648 1.11 (0.85, 1.44) 1.15 (0.87, 1.53) \\ p=0.90 Cigarette smoking $	10–19	42	52,404	1.18 (0.83, 1.66)	1.23 (0.86, 1.76)	
$p=0.88$ $p=0.90$ Cigarette smokingNever201272,257 1.00^{\ddagger} 1.00^{\ddagger} Former11681,8430.95 (0.75, 1.20) 0.89 (0.70, 1.13)Current4958,929 1.04 (0.76, 1.42) 0.97 (0.70, 1.35)Intensity of smoking** $VNever201272,2571.00^{\ddagger}1.00^{\ddagger}Former:1-14 cigs/day7360,5590.96 (0.74, 1.26)0.91 (0.69, 1.20)Former:1-14 cigs/day7360,5590.96 (0.74, 1.26)0.91 (0.69, 1.20)Current:1-14 cigs/day7360,5590.96 (0.74, 1.26)0.91 (0.69, 1.20)Former:1-14 cigs/day7360,5590.96 (0.74, 1.26)0.91 (0.69, 1.20)Current:1-14 cigs/day7360,5590.96 (0.74, 1.26)0.91 (0.69, 1.20)Current:1-14 cigs/day733039,8480.88 (0.60, 1.29)0.83 (0.56, 1.23)Current:1-14 cigs/day7012,9571.45 (0.90, 2.33)1.35 (0.83, 2.19)Pack-years of smoking**Never201272,2571.00^{\ddagger}1.00^{\ddagger}1.00^{\ddagger}1.00^{\ddagger}1.00^{\ddagger}1.00^{\ddagger}1.221.720.99 (0.75, 1.31)0.94 (0.71, 1.25)10-141821,1720.76 (0.47, 1.23)0.72 (0.44, 1.16)15-192213,7150.99 (0.63, 1.55)$	≥ 20	95	59,648	1.11 (0.85, 1.44)	1.15 (0.87, 1.53)	
Cigarette smoking Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Former 116 81,843 0.95 (0.75, 1.20) 0.89 (0.70, 1.13) Current 49 58,929 1.04 (0.76, 1.42) 0.97 (0.70, 1.35) Intensity of smoking** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Former: 1-14 cigs/day 73 60,559 0.96 (0.74, 1.26) 0.91 (0.69, 1.20) Former: 2 15 cigs/day 41 28,100 0.95 (0.67, 1.33) 0.88 (0.63, 1.25) Current: 1-14 cigs/day 30 39,848 0.88 (0.60, 1.29) 0.83 (0.56, 1.23) Current: 2 15 cigs/day 19 12,957 1.45 (0.90, 2.33) 1.35 (0.83, 2.19) Pack-years of smoking** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Sech - years of smoking ** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Sech - years of smoking ** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Sech - years of smoking ** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Sech - years of smoking ** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Sech - years of smoking ** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Sech - years of smoking ** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Sech - years of smoking ** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Sech - years of smoking ** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Sech - years of smoking ** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Sech - years of smoking ** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} Sech - years of smoking ** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} 1.00^{\ddagger} Sech - years of smoking ** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} 1.00^{\ddagger} Sech - years of smoking ** Never 201 272,257 1.00^{\ddagger} $1.$	Test for ordinal trend			<i>p</i> =0.88	<i>p</i> =0.90	
Never201 $272,257$ 1.00^{\ddagger} 1.00^{\ddagger} 1.00^{\ddagger} Former116 $81,843$ $0.95 (0.75, 1.20)$ $0.89 (0.70, 1.13)$ Current49 $58,929$ $1.04 (0.76, 1.42)$ $0.97 (0.70, 1.35)$ Intensity of smoking**Never201 $272,257$ 1.00^{\ddagger} 1.00^{\ddagger} Former: 1-14 cigs/day73 $60,559$ $0.96 (0.74, 1.26)$ $0.91 (0.69, 1.20)$ Former: 2 15 cigs/day41 $28,100$ $0.95 (0.67, 1.33)$ $0.88 (0.63, 1.25)$ Current: 1-14 cigs/day30 $39,848$ $0.88 (0.60, 1.29)$ $0.83 (0.56, 1.23)$ Current: 2 15 cigs/day19 $12,957$ $1.45 (0.90, 2.33)$ $1.35 (0.83, 2.19)$ Pack-years of smoking**Never201 $272,257$ 1.00^{\ddagger} 1.00^{\ddagger} 1065 $80,139$ $0.99 (0.75, 1.31)$ $0.94 (0.71, 1.25)$ $10-14$ 18 $21,172$ $0.76 (0.47, 1.23)$ $0.72 (0.44, 1.16)$ $15-19$ 22 $13,715$ $0.99 (0.63, 1.55)$ $0.93 (0.59, 1.46)$ ≥ 20 55 $28,888$ $1.16 (0.85, 1.57)$ $1.08 (0.79, 1.47)$	Cigarette smoking					
Former11681,8430.95 (0.75, 1.20)0.89 (0.70, 1.13)Current4958,9291.04 (0.76, 1.42)0.97 (0.70, 1.35)Intensity of smoking** 100^{\ddagger} Never201272,257 1.00^{\ddagger} 1.00^{\ddagger} Former: 1–14 cigs/day7360,5590.96 (0.74, 1.26)0.91 (0.69, 1.20)Former: ≥ 15 cigs/day4128,1000.95 (0.67, 1.33)0.88 (0.63, 1.25)Current: 1–14 cigs/day3039,8480.88 (0.60, 1.29)0.83 (0.56, 1.23)Current: $1-14$ cigs/day1912,9571.45 (0.90, 2.33)1.35 (0.83, 2.19)Pack-years of smoking** 100^{\ddagger} 1.00^{\ddagger}Never201272,2571.00^{\ddagger}1.00^{\ddagger}1.00^{\ddagger}1.00^{\ddagger}1.00^{\ddagger}1.00^{\ddagger}1.1680,1390.99 (0.75, 1.31)0.94 (0.71, 1.25)10-141821,1720.76 (0.47, 1.23)0.72 (0.44, 1.16)15–192213,7150.99 (0.63, 1.55)0.93 (0.59, 1.46)205528,8881.16 (0.85, 1.57)1.08 (0.79, 1.47)Test for ordinal trend $p=0.33$ $p=0.32$ $p=0.33$ $p=0.32$	Never	201	272,257	1.00‡	1.00≠	
Current4958,929 $1.04 (0.76, 1.42)$ $0.97 (0.70, 1.35)$ Intensity of smoking**Never201272,257 1.00^{\ddagger} 1.00^{\ddagger} Former: 1-14 cigs/day7360,559 $0.96 (0.74, 1.26)$ $0.91 (0.69, 1.20)$ Former: $\geq 15 cigs/day$ 4128,100 $0.95 (0.67, 1.33)$ $0.88 (0.63, 1.25)$ Current: 1-14 cigs/day3039,848 $0.88 (0.60, 1.29)$ $0.83 (0.56, 1.23)$ Current: $\geq 15 cigs/day$ 1912,957 $1.45 (0.90, 2.33)$ $1.35 (0.83, 2.19)$ Pack-years of smoking**Never201272,257 1.00^{\ddagger} 1.00^{\ddagger} 106580,139 $0.99 (0.75, 1.31)$ $0.94 (0.71, 1.25)$ $10-14$ 1821,172 $0.76 (0.47, 1.23)$ $0.72 (0.44, 1.16)$ $15-19$ 2213,715 $0.99 (0.63, 1.55)$ $0.93 (0.59, 1.46)$ ≥ 20 5528,888 $1.16 (0.85, 1.57)$ $1.08 (0.79, 1.47)$ Test for ordinal trend	Former	116	81,843	0.95 (0.75, 1.20)	0.89 (0.70, 1.13)	
Intensity of smoking **Never201 $272,257$ 1.00^{\ddagger} 1.00^{\ddagger} Former: 1–14 cigs/day7360,559 $0.96 (0.74, 1.26)$ $0.91 (0.69, 1.20)$ Former: ≥ 15 cigs/day41 $28,100$ $0.95 (0.67, 1.33)$ $0.88 (0.63, 1.25)$ Current: 1–14 cigs/day30 $39,848$ $0.88 (0.60, 1.29)$ $0.83 (0.56, 1.23)$ Current: ≥ 15 cigs/day19 $12,957$ $1.45 (0.90, 2.33)$ $1.35 (0.83, 2.19)$ Pack-years of smoking **Never201 $272,257$ 1.00^{\ddagger} 1.00^{\ddagger} <10	Current	49	58,929	1.04 (0.76, 1.42)	0.97 (0.70, 1.35)	
Never 201 $272,257$ $1.00^{\frac{1}{2}}$ $1.00^{\frac{1}{2}}$ Former: 1-14 cigs/day 73 60,559 0.96 (0.74, 1.26) 0.91 (0.69, 1.20) Former: ≥ 15 cigs/day 41 28,100 0.95 (0.67, 1.33) 0.88 (0.63, 1.25) Current: 1-14 cigs/day 30 39,848 0.88 (0.60, 1.29) 0.83 (0.56, 1.23) Current: ≥ 15 cigs/day 19 12,957 1.45 (0.90, 2.33) 1.35 (0.83, 2.19) Pack-years of smoking** Never Never 201 272,257 $1.00^{\frac{1}{2}}$ $1.00^{\frac{1}{2}}$ 10 65 80,139 0.99 (0.75, 1.31) 0.94 (0.71, 1.25) 10-14 18 21,172 0.76 (0.47, 1.23) 0.72 (0.44, 1.16) 15-19 22 13,715 0.99 (0.63, 1.55) 0.93 (0.59, 1.46) ≥ 20 55 28,888 1.16 (0.85, 1.57) 1.08 (0.79, 1.47)	Intensity of smoking**					
Former: $1-14 \operatorname{cigs/day}$ 73 60,559 0.96 (0.74, 1.26) 0.91 (0.69, 1.20) Former: $\geq 15 \operatorname{cigs/day}$ 41 28,100 0.95 (0.67, 1.33) 0.88 (0.63, 1.25) Current: $1-14 \operatorname{cigs/day}$ 30 39,848 0.88 (0.60, 1.29) 0.83 (0.56, 1.23) Current: $\geq 15 \operatorname{cigs/day}$ 19 12,957 1.45 (0.90, 2.33) 1.35 (0.83, 2.19) Pack-years of smoking** 1.00 [‡] 1.00 [‡] <10	Never	201	272,257	1.00‡	1.00^{\ddagger}	
Former: ≥ 15 cigs/day 41 28,100 0.95 (0.67, 1.33) 0.88 (0.63, 1.25) Current: 1-14 cigs/day 30 39,848 0.88 (0.60, 1.29) 0.83 (0.56, 1.23) Current: ≥ 15 cigs/day 19 12,957 1.45 (0.90, 2.33) 1.35 (0.83, 2.19) Pack-years of smoking** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} <10	Former: 1–14 cigs/day	73	60,559	0.96 (0.74, 1.26)	0.91 (0.69, 1.20)	
Current: $1-14 \operatorname{cigs/day}$ 30 39,848 0.88 (0.60, 1.29) 0.83 (0.56, 1.23) Current: $\geq 15 \operatorname{cigs/day}$ 19 12,957 1.45 (0.90, 2.33) 1.35 (0.83, 2.19) Pack-years of smoking** Never 201 272,257 1.00^{\ddagger} 1.00^{\ddagger} <10	Former: ≥ 15 cigs/day	41	28,100	0.95 (0.67, 1.33)	0.88 (0.63, 1.25)	
Current: $\geq 15 \text{ cigs/day}$ 1912,9571.45 (0.90, 2.33)1.35 (0.83, 2.19)Pack-years of smoking**Never201272,257 1.00^{\ddagger} 1.00^{\ddagger} <10	Current: 1–14 cigs/day	30	39,848	0.88 (0.60, 1.29)	0.83 (0.56, 1.23)	
Pack-years of smoking** Never 201 $272,257$ 1.00^{\ddagger} 1.00^{\ddagger} < 10	Current: ≥ 15 cigs/day	19	12,957	1.45 (0.90, 2.33)	1.35 (0.83, 2.19)	
Never201272,257 1.00^{\ddagger} 1.00^{\ddagger} <10	Pack-years of smoking**					
< 10 6580,1390.99 (0.75, 1.31)0.94 (0.71, 1.25) $10-14$ 18 $21,172$ $0.76 (0.47, 1.23)$ $0.72 (0.44, 1.16)$ $15-19$ 22 $13,715$ $0.99 (0.63, 1.55)$ $0.93 (0.59, 1.46)$ ≥ 20 55 $28,888$ $1.16 (0.85, 1.57)$ $1.08 (0.79, 1.47)$ Test for ordinal trend	Never	201	272,257	1.00≠	1.00≠	
$10-14$ 18 $21,172$ $0.76 (0.47, 1.23)$ $0.72 (0.44, 1.16)$ $15-19$ 22 $13,715$ $0.99 (0.63, 1.55)$ $0.93 (0.59, 1.46)$ ≥ 20 55 $28,888$ $1.16 (0.85, 1.57)$ $1.08 (0.79, 1.47)$ Test for ordinal trend $p=0.33$	< 10	65	80,139	0.99 (0.75 1 31)	0.94 (0.71 1 25)	
15-19 22 13,715 0.99 (0.63, 1.55) 0.93 (0.59, 1.46) ≥ 20 55 28,888 1.16 (0.85, 1.57) 1.08 (0.79, 1.47) Test for ordinal trend	10-14	18	21,172	0.76 (0.47, 1.23)	0.72 (0.44, 1.16)	
$\geq 20 \qquad 55 \qquad 28,888 \qquad 1.16 (0.85, 1.57) \qquad 1.08 (0.79, 1.47)$ Test for ordinal trend $p=0.33 \qquad p=0.32$	15–19	22	13,715	0.99 (0.63, 1.55)	0.93 (0.59, 1.46)	
Test for ordinal trend $p=0.33$ $p=0.32$	≥ 20	55	28,888	1.16 (0.85, 1.57)	1.08 (0.79, 1.47)	
p 0.00 D=0.02	Test for ordinal trend		-,	p=0.33	p=0.32	

Years of smoking

Characteristic	Cases	Person-years	Model 1 IRR (95%CI)*	Model 2 IRR $(95\% CI)^{\dagger}$
Never	201	272,257	1.00‡	1.00≠
1–9	31	45,282	0.97 (0.66, 1.41)	0.92 (0.63, 1.34)
10–14	15	23,214	0.80 (0.47, 1.36)	0.77 (0.45, 1.30)
15–19	20	21,617	0.97 (0.61, 1.54)	0.91 (0.57, 1.45)
≥ 20	96	53,802	1.07 (0.84, 1.38)	1.00 (0.78, 1.30)
Test for ordinal trend			<i>p</i> =0.39	<i>p</i> =0.38

*Adjusted for age and questionnaire cycle.

 † Adjusted for age, questionnaire cycle, education, cigarette smoking, current alcohol consumption, hypertension, vigorous physical activity, and energy intake. Analyses of anthropometric factors are additionally adjusted for diabetes. Analyses of diabetes, height, waist circumference, WHR, cigarette smoking and alcohol consumption are additionally adjusted for BMI. Analyses of alcohol consumption are adjusted for cigarette smoking, and analyses of cigarette smoking are adjusted for current alcohol consumption.

 ‡ Reference group.

Results for weight change are restricted to 32,305 women with complete data on weight at age 18.

 ${}^{\it f\!\!/}_{\it Results}$ for waist circumference is restricted to the 28,238 women with complete data on this measure.

[#]Results for waist-to-hip ratio are restricted to the 27,560 women with complete data on this measure.

** Excludes 33 current smokers and 184 former smokers with an unknown number of cigarettes smoked.

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		Ł	AGE <50		V	(GE ≥50	
Characteristic	Cases	Person-years	Multivariable IRR (95%CI)*	Cases	Person-years	Multivariable IRR (95%CI)*	P-value, test for age interaction $\mathring{\star}$
Type 2 diabetes							
No	90	273,351	1.00°	218	116,120	1.00°	0.26
Yes	6	7,895	2.28 (1.11, 4.66)	48	15,593	1.49 (1.08, 2.07)	
Years since diagnosis:							
< 5	4	4,810	1.67 (0.60, 4.66)	21	5,125	$1.89\ (1.19,\ 3.00)$	0.32
5-9	ю	2,162	2.86(0.88, 9.28)	10	4,972	1.14(0.60, 2.17)	
≥ 10	2	924	$3.96\ (0.94,16.7)$	17	5,497	1.38(0.83, 2.30)	
Test for ordinal trend			p=0.19			p=0.24	
ody mass index, kg/m ²							
< 25	20	98,030	1.00%	69	28,429	1.00°	0.01
25–29	38	89,084	1.65 (0.96, 2.85)	92	49,416	$0.76\ (0.55,1.04)$	
30–34	15	50,462	1.14(0.58, 2.26)	59	31,084	$0.75\ (0.52,1.08)$	
≥ 35	27	46,258	2.42(1.31, 4.44)	46	23,409	$0.83\ (0.56,1.23)$	
Test for ordinal trend			p=0.02			p=0.24	
/eight change since age 18.	, kg [§]						
< 10	20	76,891	1.00 $\hat{\tau}$	36	17,095	1.00°	0.21
10–14	12	47,167	$0.78\ (0.38,1.60)$	31	16,774	$0.82\ (0.51,1.34)$	
15-24	27	79,237	$0.89\ (0.50,1.60)$	93	41,397	$1.00\ (0.68, 1.48)$	
≥ 25	40	78,579	1.19(0.68, 2.10)	102	55,726	0.82 (0.56, 1.22)	
Test for ordinal trend			p=0.46			p=0.30	
leight, feet and inches							
< 5'3"	21	50,689	1.00^{\dagger}	68	27,809	1.00°	0.41
5'3" - 5'4"	20	71,292	0.69 (0.37, 1.28)	99	35,515	$0.76\ (0.54,1.07)$	
5'5" - 5'6"	30	77,018	$0.99\ (0.56, 1.75)$	LL	36,686	0.86 (0.62, 1.20)	
≥ 5'7"	29	84,835	$0.94\ (0.53,1.67)$	55	32,328	$0.72\ (0.50,1.03)$	
Test for ordinal trend			p=0.76			p=0.15	

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		Ą	AGE <50		V	GE ≥50	
Characteristic	Cases	Person-years	Multivariable IRR (95%CI)*	Cases	Person-years	Multivariable IRR (95%CI)*	P-value, test for age interaction \mathring{t}
Waist circumference, inches	1						
< 29	17	79,560	1.00°	46	23,824	1.00°	0.01
29–31	15	51,754	2.88 (1.16, 7.15)	51	22,548	1.08 (0.70, 1.68)	
32–34	22	58,754	2.91 (1.10, 7.72)	70	35,270	$0.93\ (0.58,1.49)$	
≥ 35	30	55,602	3.60 (1.26, 10.2)	64	33,501	$0.91\ (0.54,1.54)$	
Test for ordinal trend			p = 0.21			$p{=}0.59$	
Waist-to-hip ratio#							
< 0.72	16	60,569	1.00°	46	26,426	1.00°	0.22
0.72-0.77	27	63,152	1.52 (0.82, 2.83)	70	32,019	1.17 (0.80, 1.71)	
0.78-0.84	6	56,501	0.47 (0.20, 1.10)	57	28,733	1.12 (0.75, 1.66)	
≥ 0.85	31	59,020	1.96 (1.04, 3.67)	53	25,750	1.15 (0.76, 1.73)	
Test for ordinal trend			$p{=}0.20$			p = 0.6I	
Alcohol consumption							
Never	39	142,011	$1.00\dot{t}$	106	55,415	$1.00\mathring{r}$	0.55
Former	19	57,507	1.04 (0.58, 1.54)	71	35,490	1.03 (0.75, 1.41)	
Current	42	83,896	1.71 (1.08, 2.72)	68	41,233	1.21 (0.90, 1.63)	
Current alcohol consumptio	u						
None	58	199,518	$1.00\dot{t}$	177	90,905	$1.00\mathring{r}$	0.08
1-6 drinks per week	38	71,987	1.79~(1.18, 2.74)	67	34,070	$1.09\ (0.82, 1.46)$	
\geq 7 drinks per week	4	11,909	1.04 (0.37, 2.93)	22	7,163	1.73 (1.10, 2.74)	
Test for ordinal trend			$p{=}0.48$			p = 0.05	
Years of alcohol consumptic	uc						
Never	39	142,011	$1.00\dot{\tau}$	106	55,415	$1.00\mathring{r}$	0.20
1–9	24	72,702	1.30 (0.77, 2.20)	45	23,435	1.11 (0.78, 1.58)	
10–19	16	39,814	1.38 (0.75, 2.54)	26	12,591	1.19 (0.77, 1.86)	
≥ 20	18	22,759	1.65(0.90, 3.02)	LL	36,889	1.04 (0.76, 1.44)	
Test for ordinal trend			$p{=}0.48$			$p{=}0.58$	
Cigarette smoking							

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 1.00^{\dagger}

70,077

139

 1.00^{\uparrow}

202,179

62

Never Smoker

		7	AGE <50		Å	NGE ≥50	
Characteristic	Cases	Person-years	Multivariable IRR (95%CI) [*]	Cases	Person-years	Multivariable IRR (95%CI)*	P-value, test for age interaction ‡
Former Smoker	23	45,512	1.06 (0.65, 1.74)	93	45,503	0.86 (0.66, 1.12)	
Current Smoker	15	36,143	1.03 (0.57, 1.85)	34	16,758	$0.94\ (0.64, 1.39)$	
Intensity of smoking**							
Never	62	202,179	1.00 \mathring{r}	139	70,077	1.00°	0.43
Former: 1–14 cigs/day	17	32,763	1.14 (0.66, 1.98)	56	27,796	$0.86\ (0.63,1.18)$	
Former: ≥ 15 cigs/day	9	11,638	0.97 (0.41, 2.26)	35	16,462	0.87 (0.59, 1.26)	
Current: 1-14 cigs/day	٢	27,822	$0.64\ (0.29,1.41)$	23	12,026	0.91 (0.58, 1.44)	
Current: ≥ 15 cigs/day	8	8,256	2.26(1.05, 4.84)	Π	4,701	$1.02\ (0.54,1.92)$	
Pack-years of smoking**							
Never	62	202,179	1.00 \dot{r}	139	70,077	1.00°	0.14
< 10	20	52,766	1.05 (0.63, 1.76)	45	27,373	0.90 (0.64, 1.27)	
10–14	ю	12,506	0.47 (0.15, 1.52)	15	8,666	0.81 (0.47, 1.38)	
15–19	1	5,624	0.36(0.05,2.61)	21	8,092	$0.99\ (0.62, 1.58)$	
≥ 20	14	10,754	2.30 (1.24, 4.25)	41	18,129	$0.90\ (0.63,1.28)$	
Test for ordinal trend			$p{=}0.06$			p = 0.87	
lears of smoking							
Never	62	202,179	1.00 $\mathring{\tau}$	139	70,077	1.00^{\ddagger}	0.30
1–9	12	30,758	1.20 (0.64, 2.25)	19	14,525	$0.80\ (0.50,1.30)$	
10–14	2	16,446	$0.31\ (0.08,1.28)$	13	6,768	0.99 (0.56, 1.76)	
15–19	9	14,363	0.94 (0.40, 2.20)	14	7,254	$0.90\ (0.52,1.58)$	
≥ 20	18	20,088	1.54(0.88, 2.70)	78	33,714	$0.92\ (0.69,1.23)$	
est for ordinal trend			p=0.28			p=0.68	

additionally adjusted for diabetes. Analyses of diabetes, height, waist circumference, WHR, cigarette smoking and alcohol consumption are additionally adjusted for BMI. Analyses of alcohol consumption are adjusted for cigarette smoking, and analyses of cigarette smoking are adjusted for current alcohol consumption.

 $^{\dagger}\mathrm{Reference}$ group.

 \sharp Test for interaction using ordinal exposure variable and binary age (<50 vs. \geq 50).

 $^{\$}$ Results for weight change are restricted to 32,305 women with complete data on weight at age 18.

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 $m \chi$ Results for waist circumference is restricted to the 28,238 women with complete data on this measure.

#Results for waist-to-hip ratio are restricted to the 27,560 women with complete data on this measure.

** Excludes 33 current smokers and 184 former smokers with an unknown number of cigarettes smoked.