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Overall and Central Obesity and Risk of Lung Cancer: A Pooled Analysis

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Abstract

Background: The obesity–lung cancer association remains controversial. Concerns over confounding by smoking and reverse causation persist. The influence of obesity type and effect modifications by race/ethnicity and tumor histology are largely unexplored.

Methods: We examined associations of body mass index (BMI), waist circumference (WC), and waist-hip ratio (WHR) with lung cancer risk among 1.6 million Americans, Europeans, and Asians. Cox proportional hazard regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) with adjustment for potential confounders. Analyses for WC/WHR were further adjusted for BMI. The joint effect of BMI and WC/WHR was also evaluated.

Results: During an average 12-year follow-up, 23 732 incident lung cancer cases were identified. While BMI was generally associated with a decreased risk, WC and WHR were associated with increased risk after controlling for BMI. These associations were seen 10 years before diagnosis in smokers and never smokers, were strongest among blacks, and varied by histological type. After excluding the first five years of follow-up, hazard ratios per 5 kg/m^2 increase in BMI were 0.95 (95% CI = 0.90 to 1.00), 0.92 (95% CI = 0.89 to 0.95), and 0.89 (95% CI = 0.86 to 0.91) in never, former, and current smokers, and 0.86 (95% CI = 0.84 to 0.89), 0.94 (95% CI = 0.90 to 0.99), and 1.09 (95% CI = 1.03 to 1.15) for adenocarcinoma, squamous cell, and small cell carcinoma, respectively. Hazard ratios per 10 cm increase in WC were 1.09 (95% CI = 1.00 to 1.18), 1.12 (95% CI = 1.07 to 1.17), and 1.11 (95% CI = 1.07 to 1.16) in never, former, and current smokers, and 1.06 (95% CI = 1.01 to 1.12), 1.20 (95% CI = 1.12 to 1.29), and 1.13 (95% CI = 1.04 to 1.23) for adenocarcinoma, squamous cell, and small cell carcinoma, respectively. Participants

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with BMIs of less than 25 kg/m^2 but high WC had a 40% higher risk (HR = 1.40, 95% CI = 1.26 to 1.56) than those with BMIs of 25 kg/m^2 or greater but normal/moderate WC.
Conclusions: The inverse BMI–lung cancer association is not entirely due to smoking and reverse causation. Central obesity, particularly concurrent with low BMI, may help identify high-risk populations for lung cancer.

Obesity is a major risk factor for several common cancers (1,2). High body mass index (BMI), however, has been associated with a reduced risk of lung cancer, especially among smokers (1–5). Confounding by smoking and reverse causation due to preclinical weight loss have been considered the main explanations. However, some studies found this inverse BMI–lung cancer association among never smokers or after excluding early follow-up years (5–8), suggesting that other mechanisms may be involved. Most of the previous analyses, particularly those among never smokers, had relatively small sample sizes. Given that lung cancer is less common among never smokers, large collaborative analyses involving multiple cohort studies are needed to fully address the impact of confounding and reverse causation. On the other hand, waist circumference (WC) and waist-to-hip ratio (WHR), measures of central obesity, have been linked with increased lung cancer risk independent of BMI (7–11), although the evidence remains limited compared with that for overall obesity. It has also been suggested that the obesity–lung cancer relationship may differ by tumor histology (12,13) and race/ethnicity (14–16); yet, most prior studies have had insufficient power to examine these relationships, particularly for rare histological types and among nonwhite populations.

In a pooled analysis of 12 cohort studies from the United States, Europe, and Asia, we evaluated the associations of BMI, WC, and WHR with lung cancer risk. The large sample size, long follow-up time, and harmonized individual-level data allow us to address potential confounding and reverse causation and evaluate possible effect modifications by sex, race/ethnicity, smoking status, and histological type.

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Methods

Study Population

Twelve prospective cohort studies were included: in the United States, the National Institutes of Health–AARP study (NIH-AARP), Health Professionals Follow-Up Study (HPFS), Nurses' Health Study (NHS), Iowa Women's Health Study (IWHS), Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), Southern Community Cohort Study (SCCS), and Vitamins and Lifestyle Cohort Study (VITAL); in Europe, the European Prospective Investigation into Cancer and Nutrition Cohort (EPIC) and Nord-Trøndelag Health Study (HUNT); in Asia, the Japan Public Health Center-based Prospective Study cohort (JPHC), Shanghai Men's Health Study (SMHS), and Shanghai Women's Health Study (SWHS). Details of this consortium have been described (17). Each study was approval by its respective institutional review board, and written informed consent was obtained from the study participants. The pooling project was approved by the Vanderbilt University Institutional Review Board.

Anthropometrics Assessment

Weight and height data were collected at baseline in all participating studies, based on self-reports or measurements. Self-reported weight and height were validated in several cohorts and showed high correlations with measurements (18–20). BMI was calculated as weight (kilograms) divided by square of height (meters). According to World Health Organization (WHO) classifications (21), BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5–22.99 and 23.00–24.99 kg/m^2), overweight (25.00–27.49 and 27.50–29.99 kg/m^2), obesity class I (30.00–34.99 kg/m^2), or obesity classes II and III (≥35.0 kg/m^2).

Waist and hip circumference data were available in four US studies, two European studies, and two Asian studies, all based on tape measurements. According to WHO classifications (22), WC was categorized as less than 88.0, 88.0 to 93.9, 94.0 to 101.9, or 102 or more cm for non-Asian men, less than 80.0, 80.0 to 87.9, 88.0 to 93.9, or 94 or more cm for Asian men, and less than 72, 72.0 to 79.9, 80.0 to 87.9, 88 or more cm for all women, corresponding to normal, moderate, high, and very high WC; the last two groups were defined as central obesity. WHR was categorized as less than 0.90, 0.90 to 0.949, 0.95 to 0.99, or 1.00 or higher for non-Asian men, less than 0.85, 0.85 to 0.899, 0.90 to 0.949, or 0.95 or higher for Asian men, and less than 0.75, 0.75 to 0.799, 0.80 to 0.849, 0.85 or higher for all women, corresponding to normal, moderate, high, and very high WHR. We also conducted analyses using cohort- and sex-specific quintile cutoffs of WC and WHR, and results are shown in the Supplementary Tables 1 and 2 (available online).

Cancer Ascertainment

Incident primary cancer cases and their histology information were identified per each cohort study's protocol, mostly via follow-up surveys, linkage with cancer registries, review of medical records, or a combination of these methods. Follow-up time ended at first cancer diagnosis (any site), death, loss to follow-up, or the date of the latest follow-up, whichever came first. According to the *International Classification of Diseases* (ICD), lung cancer was ascertained by codes 162 (ICD-9) or C34 (ICD-10). Based on histology data provided by each cohort, lung cancers were classified into adenocarcinoma, squamous cell carcinoma, other non–small cell carcinoma, small cell carcinoma, and all others (including unknown).

Covariates Assessment

Baseline information on sociodemographics, smoking and other lifestyle habits, and medical history was obtained from each cohort. Harmonized covariates adjusted for in the analyses included age, sex, race/ethnicity, education, smoking status, smoking pack-years, age at smoking initiation, years since smoking cessation, family history of lung cancer, physical activity, alcohol consumption, and menopausal status in women.

Statistical Analysis

Participants were excluded if they had a history of any cancer at baseline (except nonmelanoma skin cancer), missing data on BMI or smoking status, or extreme BMI (beyond five standard

Table 1. Characteristics of the participating cohorts

Cohort	Participants, No.	Years of enrollment	Follow-up, mean, y	Incident lung cancer cases, No.	Baseline age, mean (SD), y	Women, %	Smokers, %	BMI in men, mean (SD), kg/m^2	BMI in women, mean (SD), kg/m^2	Central obesity in men*, %	Central obesity in women*, %
United States											
NIH-AARP	482 455	1995–1997	9.1	9521	61.5 (5.4)	40.0	65.8	27.3 (4.2)	26.9 (5.7)	57.4	59.7
HPFS	45 052	1986–1987	18.9	953	54.4 (9.7)	0	56.4	25.5 (3.1)	–	47.6	–
IWHS	34 743	1986–1986	18.5	1024	61.5 (4.2)	100	34.3	–	26.9 (5.1)	–	67.6
NHS	72 885	1984–1984	21.9	1831	42.2 (7.2)	100	56.1	–	25.0 (4.7)	–	–
PLCO	106 911	1993–2004	9.3	1818	63.9 (5.7)	50.4	56.7	27.6 (4.1)	27.0 (5.4)	–	–
SCCS	69 465	2002–2009	6.2	823	51.9 (8.6)	59.0	65.7	28.1 (6.1)	32.0 (8.1)	64.4	92.2
VITAL	67 380	2000–2002	8.8	1020	61.2 (7.4)	50.5	55.4	27.6 (4.4)	27.3 (5.8)	–	–
Europe											
EPIC	465 569	1991–2001	11.1	2791	50.7 (9.9)	70.0	50.1	26.5 (3.6)	25.0 (4.4)	51.0	45.1
HUNT	61 048	1995–1997	15.9	541	48.9 (16.9)	52.6	56.1	26.5 (3.5)	26.2 (4.6)	39.5	51.3
Asia											
JPHC	96 093	1990–1995	17.0	1667	52.1 (8.0)	52.1	40.4	23.5 (2.9)	23.5 (3.2)	–	–
SMHS	61 437	2001–2006	10.0	917	54.9 (9.7)	0	69.6	23.7 (3.1)	–	37.6	–
SWHS	73 319	1996–2000	15.2	826	52.0 (9.1)	100	2.8	–	24.0 (3.4)	–	40.5
Total	1 636 357	1984–2009	11.9	23 732	55.4 (10.3)	55.7	54.4	26.5 (4.1)	25.9 (5.3)	50.3	49.7

*Waist circumference data are not available in four cohorts: NHS, PLCO, VITAL, and JPHC. The number of participants with available waist circumference data is 861 133. Central obesity is defined according to World Health Organization recommendation, that is, waist circumference ≥94 cm for non-Asian men, ≥90 cm for Asian men, and ≥80 cm for all women. BMI = body mass index; EPIC = European Prospective Investigation into Cancer and Nutrition Cohort; HUNT = The Nord-Trøndelag Health Study; HPFS = Health Professionals Follow-Up Study; IWHS = Iowa Women's Health Study; JPHC = Japan Public Health Center-based Prospective Study; NHS = Nurses' Health Study; NIH-AARP = National Institutes of Health-AARP Study; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SCCS = Southern Community Cohort Study; SMHS = Shanghai Men's Health Study; SWHS = Shanghai Women's Health Study; VITAL = Vitamins and Lifestyle Study.

deviations of the cohort- and sex-specific log-transformed mean).

Baseline characteristics across BMI categories were compared using a general linear model for continuous variables and the chi-square test for categorical variables. The Cox proportional hazard model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) with stratification by cohort, enrollment year, and birth year, and adjustment for all covariates listed above. Analyses for WC/WHR were further adjusted for BMI categories; results without adjustment for BMI are also shown in Supplementary Tables 3 and 4 (available online). The proportional hazard assumption was tested using the Schoenfeld residual method. In addition, we evaluated the joint effect of overall and central obesity by grouping participants into four categories according to their BMI (< or ≥25 kg/m^2) and WC/WHR (normal/moderate or high/very high).

These obesity measures were also modeled as continuous variables; hazard ratios were estimated for each 5 kg/m^2 increase in BMI, 10 cm increase in WC, and 0.1 increase in WHR. To avoid the influence of extreme values, participants with BMI lower than 15 or higher than 50 kg/m^2 or WC/WHR in the sex-specific top and bottom 1% were excluded from these analyses.

Analyses were conducted by years of follow-up, sex, race/ethnicity, smoking status, and histological type. Potential interaction was evaluated via likelihood ratio test comparing models with and without the interaction terms. We also conducted meta-analyses to combine results from each cohort. Potential heterogeneity was evaluated across cohorts, follow-up time intervals, and histological types using Cochran's Q (23). Sensitivity analyses were further performed, including additional adjustment for passive smoking among cohorts that collected this information and additional adjustment for dietary intakes of saturated and polyunsaturated fats, given that we recently reported their associations with lung cancer risk in this pooling project (24). All analyses were conducted using SAS, version 9.4. All statistical tests were two-sided, and a *P* value of less than .05 was considered statistically significant.

Results

Among 1 636 357 study participants (mean age at baseline = 55.4 years), 23 732 incident primary lung cancer cases were identified during an average follow-up of 11.9 years. As shown in Table 1, average BMIs were higher in the US and European cohorts (25.0–32.0 kg/m^2) than in Asian cohorts (23.5–24.0 kg/m^2). Among 861 133 participants with WC data, 50.3% of men and 49.7% of women had central obesity, according to WHO definitions. Overweight and obesity were more common among blacks, individuals without college education, former smokers, heavy smokers (>50 pack-years), and individuals with a family history of lung cancer and low physical activity level (Table 2). As expected, WC and WHR increased substantially from normal weight to obese groups and were similarly associated with the above-mentioned factors.

BMI was inversely associated with lung cancer risk (Table 3). The association attenuated with increasing length of follow-up ($P_{heterogeneity}$ across time intervals < .001), but remained statistically significant after excluding the first five or 10 years of follow-up. To reduce potential influence of reverse causation on risk estimates, we excluded the first five years of follow-up in all remaining analyses for BMI. Among 1 482 599 participants who were alive, cancer-free, and followed for five or more years, 15 356 incident lung cancer cases were identified. Overweight (BMI = 25–29.99 kg/m^2) and class I obesity (BMI = 30–34.99 kg/m^2) were associated with lower risk of lung cancer than BMI of 23 to 24.99 kg/m^2, with hazard ratios ranging from 0.76 to 0.93 (Table 4). The association was similar in men and women, but

Table 2. Baseline characteristics across categories of body mass index

Characteristics	BMI, kg/m^2						
	<18.5	18.5–22.99	23.00–24.99	25.00–27.49	27.50–29.99	30.00–34.99	≥35.0
Participants, No.	23 865	397 759	326 328	379 523	227 165	200 482	81 235
Age at baseline, mean (SD), y	53.0 (11.8)	52.4 (11.1)	55.0 (10.4)	56.6 (9.8)	57.3 (9.4)	57.5 (9.1)	56.6 (8.8)
Female, %	70.4	69.9	54.9	46.0	45.2	51.9	68.1
Race/ethnicity, %							
White	61.3	73.4	77.8	82.2	85.3	86.6	79.3
Black	3.0	2.1	2.5	3.5	4.8	7.9	17.7
Asian	35.1	23.9	18.8	13.2	8.6	4.0	1.0
Other	0.6	0.6	0.9	1.2	1.3	1.5	2.0
College education, %	28.4	32.4	33.1	32.1	28.8	25.5	21.2
Smoking status, %							
Never	48.8	50.7	47.1	43.2	41.6	41.9	45.2
Former	18.6	24.7	32.2	38.5	41.7	42.9	41.0
Current	32.7	24.5	20.7	18.3	16.7	15.3	13.8
Cigarette smoking pack-years, %							
<30	66.7	72.4	69.0	64.5	61.2	58.2	58.9
30–50	22.6	19.1	20.2	21.7	22.6	22.8	21.2
>50	10.8	8.6	10.8	13.8	16.2	19.0	19.9
Family history of lung cancer, %	5.3	5.3	5.9	7.2	8.0	8.9	10.0
Physical activity level, %							
Low	30.0	19.4	17.5	17.3	18.2	22.3	36.8
Middle	33.2	35.9	36.4	38.3	40.9	42.2	38.0
High	36.8	44.8	46.0	44.5	40.9	35.5	25.2
Alcohol drinking status, %							
None	42.9	31.8	29.8	29.1	29.9	33.6	45.5
Moderate	42.1	51.3	54.2	55.6	55.2	53.7	46.3
Heavy	15.0	16.9	16.1	15.4	14.8	12.7	8.2
WC* in men, mean (SD), cm	74.9 (10.1)	82.8 (6.7)	89.1 (5.9)	94.3 (6.3)	100.2 (6.8)	107.6 (7.9)	121.6 (11.3)
WC* in women, mean (SD), cm	65.7 (6.1)	71.8 (5.9)	77.9 (6.3)	83.2 (7.1)	88.9 (7.7)	96.1 (8.9)	109.2 (12.6)
WHR* in men, mean (SD)	0.85 (0.07)	0.89 (0.06)	0.92 (0.06)	0.94 (0.06)	0.96 (0.06)	0.98 (0.07)	1.00 (0.08)
WHR* in women, mean (SD)	0.75 (0.06)	0.77 (0.06)	0.79 (0.06)	0.81 (0.07)	0.83 (0.07)	0.85 (0.07)	0.87 (0.08)

*Waist circumference data are available in 395 088 men and 466 045 women. Waist-to-hip ratio data are available in 384 423 men and 465 343 women. BMI = body mass index; WC = waist circumference; WHR = waist-to-hip ratio.

stronger in smokers than never smokers ($P_{interaction}$ = .006). Hazard ratios per 5 kg/m^2 increase in BMI were 0.95 (95% CI = 0.90 to 1.00), 0.92 (95% CI = 0.89 to 0.95), and 0.89 (95% CI = 0.86 to 0.91) in never, former, and current smokers, respectively. The association was stronger in blacks (HR per 5 kg/m^2 increase = 0.76, 95% CI = 0.68 to 0.84) than whites (HR per 5 kg/m^2 increase = 0.91, 95% CI = 0.89 to 0.93) and Asians (HR per 5 kg/m^2 increase = 0.93, 95% CI = 0.87 to 0.99, $P_{interaction}$ = .01). Inverse associations were found for all types of non–small cell lung cancer, with the strongest observed for adenocarcinoma (HR per 5 kg/m^2 increase = 0.86, 95% CI = 0.84 to 0.89). Notably, BMI was positively associated with risk of small cell carcinoma, with a hazard ratio per 5 kg/m^2 increase of 1.09 (95% CI = 1.03 to 1.15, $P_{heterogeneity}$ across histological types < .001).

WC and WHR were associated with increased lung cancer risk after controlling for BMI. Hazard ratios comparing very high vs normal WC/WHR ranged from 1.22 to 1.52, and each 10 cm increase in WC and 0.1 increase in WHR were associated with hazard ratios of 1.06 to 1.39 (Tables 5 and 6). The WC/WHR–lung cancer associations did not vary by follow-up time and were not modified by sex and smoking status, but the associations appeared stronger in blacks and whites than Asians and for squamous cell carcinoma than other types. Each 10 cm increase in WC was associated with hazard ratios of 1.09 (95% CI = 1.00 to 1.18), 1.12 (95% CI = 1.07 to 1.17), and 1.11 (95% CI = 1.07 to 1.16) in never, former, and current smokers, 1.24 (95% CI = 1.02 to 1.52), 1.12 (95% CI = 1.09 to 1.16), and 1.00 (95% CI = 0.92 to 1.10) in blacks, whites, and Asians, and 1.06 (95% CI = 1.01 to 1.12), 1.20 (95% CI = 1.12 to 1.29), and 1.13 (95% CI = 1.04 to 1.23) for adenocarcinoma, squamous cell carcinoma, and small cell carcinoma, respectively. Notably, very high vs normal WC showed a hazard ratio of 1.57 (95% CI = 1.28 to 1.92) for squamous cell lung cancer. WHR results were similar to WC results (Table 6). Consistent results were found when we used cohort- and sex-specific quintiles as cutoffs, instead of WHO criteria (Supplementary Tables 1 and 2, available online). Analyses without adjustment for BMI showed that WHR was positively associated with lung cancer risk with a smaller effect size; WC was weakly but inversely associated with lung cancer risk (Supplementary Tables 3 and 4, available online).

When BMI and WC/WHR were considered jointly, participants who had BMI of less than 25 kg/m^2 but high or very high WC showed a hazard ratio of 1.40 (95% CI = 1.26 to 1.56) compared with those who had BMI of 25 kg/m^2 or higher but normal or moderate WC. The joint effect of overall and central obesity on lung cancer risk did not differ by sex, race, smoking status, or histological type (Figures 1 and 2). Characteristics of participants with different obesity types are shown in Supplementary Table 5 (available online).

We also evaluated the associations within each cohort and then conducted random-effects meta-analyses (Supplementary

Table 3. Associations of lung cancer with body mass index, waist circumference, and waist-to-hip ratio by years of follow-up*,†

Anthropometric variable	Entire follow-up time, y		0–5		5–10		>10	
	Cases, No.	HR (95% CI)	Cases, No.	HR (95% CI)	Cases, No.	HR (95% CI)	Cases, No.	HR (95% CI)
BMI, kg/m^2								
<18.5	531	1.34 (1.23 to 1.47)	217	1.64 (1.42 to 1.90)	183	1.21 (1.04 to 1.41)	131	1.15 (0.96 to 1.38)
18.5–22.99	6060	1.09 (1.05 to 1.13)	1919	1.18 (1.10 to 1.26)	2125	1.03 (0.97 to 1.10)	2016	1.06 (0.99 to 1.14)
23.00–24.99	4817	1 (referent)	1560	1 (referent)	1905	1 (referent)	1352	1 (referent)
25.00–27.49	5609	0.94 (0.91 to 0.98)	2037	0.96 (0.90 to 1.03)	2227	0.90 (0.84 to 0.95)	1345	0.98 (0.91 to 1.06)
27.50–29.99	3188	0.89 (0.85 to 0.93)	1233	0.90 (0.84 to 0.98)	1300	0.84 (0.79 to 0.91)	655	0.96 (0.87 to 1.05)
30.00–34.99	2661	0.85 (0.81 to 0.90)	1071	0.85 (0.79 to 0.92)	1100	0.81 (0.75 to 0.87)	490	0.93 (0.83 to 1.03)
≥35.0	866	0.78 (0.72 to 0.84)	339	0.70 (0.62 to 0.79)	382	0.81 (0.72 to 0.90)	145	0.92 (0.77 to 1.09)
Per 5-unit increase‡		0.89 (0.88 to 0.91)		0.85 (0.83 to 0.88)		0.90 (0.88 to 0.92)		0.93 (0.90 to 0.97)
WC§								
Normal	2088	1 (referent)	732	1 (referent)	871	1 (referent)	485	1 (referent)
Moderate	2696	1.00 (0.94 to 1.06)	859	0.95 (0.86 to 1.06)	1129	1.00 (0.91 to 1.10)	708	1.05 (0.92 to 1.19)
High	2841	1.10 (1.03 to 1.18)	930	1.06 (0.94 to 1.19)	1183	1.11 (0.99 to 1.23)	728	1.16 (1.01 to 1.34)
Very high	3052	1.26 (1.16 to 1.37)	1096	1.27 (1.11 to 1.46)	1272	1.24 (1.09 to 1.40)	684	1.27 (1.07 to 1.51)
Per 10 cm increase‡		1.11 (1.08 to 1.14)		1.11 (1.06 to 1.17)		1.13 (1.08 to 1.18)		1.08 (1.01 to 1.15)
WHR§								
Normal	1646	1 (referent)	589	1 (referent)	667	1 (referent)	390	1 (referent)
Moderate	2934	1.09 (1.02 to 1.15)	905	0.97 (0.87 to 1.07)	1267	1.17 (1.07 to 1.29)	762	1.11 (0.98 to 1.25)
High	2861	1.16 (1.09 to 1.23)	929	1.10 (0.99 to 1.23)	1177	1.21 (1.09 to 1.33)	755	1.15 (1.01 to 1.30)
Very high	2993	1.28 (1.19 to 1.37)	1070	1.28 (1.14 to 1.43)	1241	1.34 (1.21 to 1.49)	682	1.15 (1.00 to 1.33)
Per 0.1 increase‡		1.14 (1.11 to 1.18)		1.18 (1.11 to 1.25)		1.16 (1.10 to 1.22)		1.08 (1.00 to 1.16)

*Cox regression analyses were carried out with stratification by cohort, year of enrollment (five-year intervals from <1985 to >2005), and year of birth (five-year intervals from <1925 to >1960), and adjustment for age, sex, race/ethnicity (white, black, Asian, or other), educational attainment (≤high school, vocational school or some college, college or graduate school), smoking history (never, former, or current use of cigarettes, cigars, or pipe), pack-years of cigarette smoking, age of smoking initiation, years since smoking cessation, family history of lung cancer (yes, no, or unknown), physical activity level (low, middle, or high, measured by metabolic equivalents or hours of exercise), alcohol consumption (none, moderate, or heavy [>14 g/d for women and >28 g/d for men]), and, in women, menopausal status (pre or post). Analyses for WC or WHR were further adjusted for BMI category. BMI = body mass index; CI = confidence interval; HR = hazard ratio; WC = waist circumference; WHR = waist-to-hip ratio.

†Potential heterogeneity was evaluated using Cochran's Q test. Two-sided $P_{heterogeneity}$ values across time intervals were <.001 for BMI, .55 for WC, and .13 for WHR.

‡To avoid influence of extreme values, participants with BMI <15 or >50 kg/m^2 or in the top and bottom 1% of WC/WHR were excluded from the analyses in which these exposures were examined.

§Normal, moderate, high, and very high WC were defined as <88.0, 88.0-93.9, 94.0–101.9, or ≥102 cm for non-Asian men, <80.0, 80.0–87.9, 88.0–93.9, or ≥94 cm for Asian men, and <72, 72.0–79.9, 80.0–87.9, ≥88 cm for all women. Normal, moderate, high, and very high WHR were defined as <0.90, 0.90–0.949, 0.95–0.99, or ≥1.00 for non-Asian men, <0.85, 0.85–0.899, 0.90–0.949, or ≥0.95 for Asian men, and <0.75, 0.75–0.799, 0.80–0.849, ≥0.85 for all women.

Figure 1, available online). Low to moderate heterogeneities across cohorts were found for the BMI–lung cancer association; the WC/WHR–lung cancer associations appeared more heterogeneous across cohorts, especially between the SMHS (all Asian men) and SCCS (all African Americans). Nevertheless, results from using pooled or meta-analyses were basically the same. Further adjustment for passive smoking status or saturated and polyunsaturated fat intakes did not change the results.

Discussion

In this pooled analysis of 12 cohort studies with more than 1.6 million individuals from the United States, Europe, and Asia, we found an overall inverse association between BMI and lung cancer, which was modified by smoking status and follow-up time, to be strongest among blacks and different between small cell and non–small cell lung cancer. Notably, the inverse association between BMI and non–small cell lung cancer was observed among never smokers after excluding the first five years of follow-up; however, BMI was positively associated with risk of small cell lung cancer. In contrast, WC and WHR were associated with increased lung cancer risk, regardless of sex, smoking status, follow-up time, and tumor histology. The WC–lung cancer association seemed particularly evident for squamous cell carcinoma. When considered jointly, participants with low/normal BMI but high/very high WC showed a 40.0% greater risk of lung cancer than those with high BMI but normal/moderate WC.

The inverse association between BMI and lung cancer has been consistently reported in many cohort studies (2,6–8,10,11,25,26), but its interpretation remains controversial. The obesity–lung cancer association is sensitive to confounding by smoking and reverse causation (27,28). Tobacco smoking, the dominant risk factor for lung cancer, usually leads to lower body weight and may also change body composition and fat distribution (29). Therefore, it is critical to carefully control for smoking exposure when evaluating the obesity–lung cancer relationships. Many studies have suggested that the inverse association of BMI with lung cancer is restricted to smokers (1,2,6,10,26), suggesting the possibility of confounding by smoking. However, other studies and two meta-analyses found a statistically significant inverse association among never smokers (3,5,7,8), consistent with our findings. Because lung cancer is relatively rare among never smokers, the statistical power to investigate the association among never smokers while addressing reverse causation has been limited. Findings from our large pooled analysis suggest that overweight and class I obesity are associated with lower lung cancer risk among both

Table 4. Associations of lung cancer with body mass index, excluding the first 5 years of follow-up, by sex, smoking status, race, and tumor histology*,†

BMI and stratified variable	Case/ participant, No.	HR (95% CI)	Case/ participant, No.	HR (95% CI)	Case/ participant, No.	HR (95% CI)
Sex	All participants (n = 1 482 599)		Men (n = 639 228)		Women (n = 843 371)	
BMI, kg/m^2						
<18.5	314/21 277	1.19 (1.06 to 1.33)	118/5974	1.23 (1.02 to 1.49)	196/15 303	1.15 (0.99 to 1.33)
18.5–22.99	4141/368 075	1.04 (1.00 to 1.09)	1654/106 570	1.09 (1.02 to 1.17)	2487/261 505	1.02 (0.96 to 1.09)
23.00–24.99	3257/299 442	1 (referent)	1640/131 378	1 (referent)	1617/168 064	1 (referent)
25.00–27.49	3572/344 028	0.93 (0.89 to 0.98)	2065/181 584	0.93 (0.87 to 0.99)	1507/162 444	0.93 (0.87 to 1.00)
27.50–29.99	1955/203 765	0.89 (0.84 to 0.94)	1160/109 309	0.88 (0.82 to 0.95)	795/94 456	0.88 (0.81 to 0.96)
30.00–34.99	1590/177 117	0.86 (0.80 to 0.91)	889/82 968	0.89 (0.81 to 0.96)	701/94 149	0.81 (0.74 to 0.88)
≥35.0	527/68 895	0.85 (0.77 to 0.93)	228/21 445	0.92 (0.80 to 1.06)	299/47 450	0.79 (0.70 to 0.90)
Per 5-unit increase‡		0.91 (0.90 to 0.93)		0.91 (0.88 to 0.94)		0.91 (0.88 to 0.93)
Smoking status	Never smokers (n = 692 717)		Former smokers (n = 503 115)		Current smokers (n = 286 767)	
BMI, kg/m^2						
<18.5	44/10 803	0.91 (0.67 to 1.24)	53/3755	1.42 (1.07 to 1.87)	217/6719	1.24 (1.08 to 1.43)
18.5–22.99	670/190 352	0.94 (0.84 to 1.05)	907/89 535	1.11 (1.01 to 1.22)	2564/88 188	1.07 (1.00 to 1.14)
23.00–24.99	555/144 143	1 (referent)	988/94 420	1 (referent)	1714/60 879	1 (referent)
25.00–27.49	504/152 391	0.90 (0.80 to 1.01)	1388/129 453	0.94 (0.87 to 1.03)	1680/62 184	0.93 (0.87 to 0.99)
27.50–29.99	241/87 048	0.83 (0.71 to 0.97)	887/83 183	0.92 (0.84 to 1.01)	827/33 534	0.87 (0.80 to 0.94)
30.00–34.99	175/76 212	0.81 (0.68 to 0.96)	778/74 661	0.87 (0.79 to 0.96)	637/26 244	0.85 (0.77 to 0.93)
≥35.0	62/31 768	0.86 (0.66 to 1.13)	275/28 108	0.88 (0.76 to 1.00)	190/9019	0.82 (0.71 to 0.96)
Per 5-unit increase‡		0.95 (0.90 to 1.00)		0.92 (0.89 to 0.95)		0.89 (0.86 to 0.91)
Race	Whites (n = 1 182 337)		Asians (n = 229 293)		Blacks (n = 55 949)	
BMI, kg/m^2						
<18.5	189/12 998	1.20 (1.03 to 1.39)	115/7686	1.20 (0.98 to 1.46)	8/471	-
18.5–22.99	2898/269 959	1.05 (0.99 to 1.11)	1129/89 673	1.06 (0.96 to 1.16)	165/12 792	1 (referent)
23.00–24.99	2501/232 475	1 (referent)	673/57 936	1 (referent)		
25.00–27.49	2937/282 258	0.92 (0.87 to 0.97)	694/65 803	0.90 (0.82 to 0.98)	167/19 205	0.76 (0.61 to 0.95)
27.50–29.99	1681/174 131	0.87 (0.82 to 0.93)				
30.00–34.99	1427/154 611	0.84 (0.79 to 0.90)	98/8195	1.02 (0.83 to 1.26)	91/23 481	0.48 (0.36 to 0.62)
≥35.0	478/55 905	0.86 (0.78 to 0.95)				
Per 5-unit increase‡		0.91 (0.89 to 0.93)		0.93 (0.87 to 0.99)		0.76 (0.68 to 0.84)
Tumor histology	Adenocarcinoma cases (n = 5921)		Squamous cell carcinoma cases (n = 2580)		Small cell carcinoma cases (n = 1914)	
BMI, kg/m^2						
<18.5	131/21 094	1.29 (1.07 to 1.54)	54/21 017	1.23 (0.93 to 1.63)	25/20 988	0.74 (0.50 to 1.12)
18.5–22.99	1705/365 639	1.05 (0.97 to 1.13)	646/364 580	0.99 (0.88 to 1.11)	459/364 393	0.94 (0.82 to 1.08)
23.00–24.99	1291/297 476	1 (referent)	544/296 729	1 (referent)	377/296 562	1 (referent)
25.00–27.49	1380/341 836	0.94 (0.87 to 1.01)	603/341 059	0.92 (0.82 to 1.04)	430/340 886	0.99 (0.86 to 1.13)
27.50–29.99	696/202 506	0.84 (0.77 to 0.93)	346/202 156	0.91 (0.80 to 1.05)	308/202 118	1.24 (1.07 to 1.45)
30.00–34.99	540/176 067	0.76 (0.69 to 0.84)	294/175 821	0.93 (0.80 to 1.07)	234/175 761	1.10 (0.93 to 1.30)
≥35.0	178/68 546	0.70 (0.60 to 0.83)	93/68 461	0.91 (0.73 to 1.14)	81/68 449	1.12 (0.88 to 1.44)
Per 5-unit increase‡		0.86 (0.84 to 0.89)		0.94 (0.90 to 0.99)		1.09 (1.03 to 1.15)

*Cox regression analyses were carried out with stratification by cohort, year of enrollment (five-year intervals from <1985 to >2005), and year of birth (five-year intervals from <1925 to >1960), and adjustment for age, sex, race/ethnicity (white, black, Asian, or other), educational attainment (≤high school, vocational school or some college, college or graduate school), smoking history (never, former, or current use of cigarettes, cigars, or pipe), pack-years of cigarette smoking, age of smoking initiation, years since smoking cessation, family history of lung cancer (yes, no, or unknown), physical activity level (low, middle, or high, measured by metabolic equivalents or hours of exercise), alcohol consumption (none, moderate, or heavy [>14 g/d for women and >28 g/d for men]), and, in women, menopausal status (pre or post). BMI = body mass index; CI = confidence interval; HR = hazard ratio.

†Potential interaction was evaluated via likelihood ratio test comparing models with and without the interaction terms. Potential heterogeneity was evaluated using Cochran's Q test. Two-sided $P_{interaction}$ values were .34 for BMI categories with sex, .006 with smoking status, and .01 with race/ethnicity. $P_{heterogeneity}$ between histological types was <.001.

‡To avoid influence of extreme values, participants with BMI <15 or >50 kg/m^2 were excluded from analysis.

smokers and never smokers, suggesting that the observed inverse BMI–lung cancer association is not entirely due to confounding by smoking. Analyses by lung cancer subtypes showed inverse associations for adenocarcinoma and squamous cell carcinoma, but a positive association for small cell lung cancer, suggesting that obesity may affect lung cancer histological types differently. These data also indicate that the obesity epidemic is not a contributing factor to the recent increase in lung adenocarcinoma risk among smokers (30).

Another putative explanation for the inverse BMI–lung cancer association is reverse causation. While chronic lung damage and lung function decline caused by smoking and other carcinogenic exposures can lead to weight loss that precedes lung cancer diagnosis (31,32) cancer itself can also cause weight loss, an effect referred to as reverse causation. However, our primary risk analyses were carried out after excluding the first five years after BMI assessment. Moreover, the inverse association persisted after excluding the first 10 years, which argues against

Table 5. Associations of lung cancer with waist circumference, by sex, smoking status, race, and tumor histology*,†,‡

WC and stratified variable	Case/participant, No.	HR (95% CI)	Case/participant, No.	HR (95% CI)	Case/participant, No.	HR (95% CI)
Sex	All participants (n = 861 133)		Men (n = 395 088)		Women (n = 466 045)	
WC						
Normal	2088/190 860	1 (referent)	1289/88 649	1 (referent)	799/102 211	1 (referent)
Moderate	2696/240 066	1.00 (0.94 to 1.06)	1469/107 788	0.97 (0.89 to 1.05)	1227/132 278	1.05 (0.95 to 1.15)
High	2841/215 247	1.10 (1.03 to 1.18)	1675/106 117	1.14 (1.04 to 1.24)	1166/109 130	1.06 (0.95 to 1.18)
Very high	3052/214 960	1.26 (1.16 to 1.37)	1652/92 534	1.27 (1.14 to 1.41)	1400/122 426	1.22 (1.08 to 1.39)
Per 10 cm increase§		1.11 (1.08 to 1.14)		1.11 (1.06 to 1.15)		1.11 (1.06 to 1.16)
Smoking status	Never smokers (n = 408 738)		Former smokers (n = 274 453)		Current smokers (n = 177 942)	
WC						
Normal	305/95 251	1 (referent)	534/49 723	1 (referent)	1249/45 886	1 (referent)
Moderate	500/117 161	1.04 (0.89 to 1.21)	858/71 671	0.97 (0.86 to 1.08)	1338/51 234	1.00 (0.92 to 1.09)
High	478/98 854	1.13 (0.94 to 1.35)	1090/74 086	1.08 (0.96 to 1.22)	1273/42 307	1.11 (1.01 to 1.22)
Very high	400/97 472	1.21 (0.97 to 1.51)	1381/78 973	1.25 (1.09 to 1.43)	1271/38 515	1.29 (1.14 to 1.44)
Per 10 cm increase§		1.09 (1.00 to 1.18)		1.12 (1.07 to 1.17)		1.11 (1.07 to 1.16)
Race	Whites (n = 706 018)		Asians (n = 137 878)		Blacks (n = 11 682)	
WC						
Normal	1587/153 891	1 (referent)	443/34 115	1 (referent)	35/1816	1 (referent)
Moderate	2087/187 386	1.03 (0.96 to 1.10)	571/49 596	0.88 (0.77 to 1.02)	21/1741	0.77 (0.43 to 1.37)
High	2339/177 400	1.13 (1.05 to 1.22)	452/34 031	0.97 (0.81 to 1.16)	31/2386	1.03 (0.58 to 1.83)
Very high	2675/187 341	1.31 (1.20 to 1.44)	309/20 136	1.01 (0.81 to 1.27)	51/5739	1.46 (0.78 to 2.73)
Per 10 cm increase§		1.12 (1.09 to 1.16)		1.00 (0.92 to 1.10)		1.24 (1.02 to 1.52)
Tumor histology	Adenocarcinoma cases (n = 3762)		Squamous cell carcinoma cases (n = 1727)		Small cell carcinoma cases (n = 1284)	
WC						
Normal	777/189 549	1 (referent)	298/189 070	1 (referent)	229/189 001	1 (referent)
Moderate	1007/238 377	0.96 (0.87 to 1.06)	402/237 772	1.09 (0.93 to 1.28)	284/237 654	0.95 (0.79 to 1.14)
High	993/213 399	1.02 (0.91 to 1.14)	482/212 888	1.34 (1.12 to 1.59)	335/212 741	1.07 (0.87 to 1.31)
Very high	985/212 893	1.12 (0.98 to 1.28)	545/212 453	1.57 (1.28 to 1.92)	436/212 344	1.23 (0.98 to 1.56)
Per 10 cm increase§		1.06 (1.01 to 1.12)		1.20 (1.12 to 1.29)		1.13 (1.04 to 1.23)

*Cox regression analyses were carried out with stratification by cohort, year of enrollment (five-year intervals from <1985 to >2005), and year of birth (five-year intervals from <1925 to >1960), and adjustment for age, sex, race/ethnicity (white, black, Asian, or other), educational attainment (≤high school, vocational school or some college, college or graduate school), smoking history (never, former, or current use of cigarettes, cigars, or pipe), pack-years of cigarette smoking, age of smoking initiation, years since smoking cessation, family history of lung cancer (yes, no, or unknown), physical activity level (low, middle, or high, measured by metabolic equivalents or hours of exercise), alcohol consumption (none, moderate, or heavy [>14 g/d for women and >28 g/d for men]), BMI category, and, in women, menopausal status (pre or post). CI = confidence interval; HR = hazard ratio; WC = waist circumference.

†Normal, moderate, high, and very high WC were defined as <88.0, 88.0–93.9, 94.0–101.9, or ≥102 cm for non-Asian men, <80.0, 80.0–87.9, 88.0–93.9, or ≥94 cm for Asian men, and <72, 72.0–79.9, 80.0–87.9, ≥88 cm for all women.

‡Potential interaction was evaluated via likelihood ratio test comparing models with and without the interaction terms. Potential heterogeneity was evaluated using Cochran's Q test. Two-sided $P_{interaction}$ values were .10 for WC categories with sex, .33 with smoking status, and .73 with race/ethnicity. $P_{heterogeneity}$ between histological types was .15.

§To avoid influence of extreme values, participants at the top and bottom 1% of WC were excluded from analysis.

reverse causation as a sole explanation. Potential biological mechanisms such as reduced levels of carcinogen-DNA adducts, oxidative DNA damage, and chromosome damage have been proposed to explain how high BMI may protect against lung carcinogenesis (4,33–35). However, these mechanisms have also been proposed for positive associations between BMI and other cancers. Well-designed, prospective studies, particularly those incorporating biomarkers for oxidative stress, inflammation, and DNA damage, may help us to better understand the biological mechanism(s) underlying the BMI–lung cancer association.

Our findings on central obesity agree with those of a recent meta-analysis of six prospective cohort studies showing that each 10 cm increase in WC was associated with a 10.0% increase in lung cancer risk (9). That meta-analysis, however, was limited by its inability to conduct subgroup analyses (e.g., by sex or histological type), control for confounding factors, or evaluate reverse causation. Our study, including nearly twice as many cases as the meta-analysis, is thus by far the largest and most comprehensive prospective investigation on central obesity and lung cancer risk.

The positive association of central obesity with lung cancer risk across sexes, races, and histological types highlights the importance of examining body composition (eg, fat vs lean mass), fat distribution (eg, central/upper vs lower body fat and subcutaneous vs visceral fat), as well as obesity-related metabolic disorders in lung carcinogenesis. At a given BMI (a rough measure of overall obesity including both fat and lean mass), individuals with high WC/WHR may have increased abdominal and visceral fat, but decreased lean mass (and thus may still maintain normal weight); meanwhile, they may manifest hyperglycemia, insulin resistance, dyslipidemia, inflammation, and altered levels of insulin-like growth factors, sex hormones, adipokines, and myokines (36,37). All of these metabolic disorders have been suggested as potential risk factors or underlying mechanisms for lung carcinogenesis, though much evidence remains inconclusive (38–41). The "low BMI–high WC" phenotype is particularly common among current and heavy smokers (as shown in Supplementary Table 5, available online), as smoking can cause many of these metabolic disorders, along with weight loss (especially muscle loss) and accumulation of

Table 6. Associations of lung cancer with waist-hip ratio, by sex, smoking status, race, and tumor histology*,†,‡

WHR and stratified variable	Cases/participants, No.	HR (95% CI)	Cases/participants, No.	HR (95% CI)	Cases/participants, No.	HR (95% CI)
Sex	All participants (n = 849 766)		Men (n = 384 423)		Women (n = 465 343)	
WHR						
Normal	1646/188 591	1 (referent)	1051/91 009	1 (referent)	595/97 582	1 (referent)
Moderate	2934/258 507	1.09 (1.02 to 1.15)	1772/123 500	1.08 (1.00 to 1.17)	1162/135 007	1.11 (1.01 to 1.23)
High	2861/219 546	1.16 (1.09 to 1.23)	1643/100 194	1.16 (1.07 to 1.26)	1218/119 352	1.16 (1.05 to 1.29)
Very high	2993/183 122	1.28 (1.19 to 1.37)	1387/69 720	1.24 (1.13 to 1.35)	1606/113 402	1.33 (1.20 to 1.47)
Per 0.1 increase§		1.14 (1.11 to 1.18)		1.13 (1.07 to 1.19)		1.16 (1.10 to 1.21)
Smoking status	Never smokers (n = 405 706)		Former smokers (n = 267 356)		Current smokers (n = 176 704)	
WHR						
Normal	228/93 163	1 (referent)	523/56 387	1 (referent)	895/39 041	1 (referent)
Moderate	494/122 919	1.11 (0.95 to 1.30)	1056/82 599	1.14 (1.02 to 1.26)	1384/52 989	1.04 (0.95 to 1.13)
High	514/104 279	1.12 (0.95 to 1.32)	1027/68 294	1.22 (1.10 to 1.36)	1320/46 973	1.11 (1.01 to 1.21)
Very high	432/85 345	1.13 (0.94 to 1.35)	1108/60 076	1.30 (1.16 to 1.45)	1453/37 701	1.30 (1.19 to 1.43)
Per 0.1 increase§		1.04 (0.95 to 1.14)		1.13 (1.07 to 1.19)		1.19 (1.13 to 1.25)
Race	Whites (n = 695 553)		Asians (n = 137 753)		Blacks (n = 11 186)	
WHR						
Normal	1331/165 532	1 (referent)	268/19 453	1 (referent)	33/2636	1 (referent)
Moderate	2378/210 794	1.11 (1.04 to 1.19)	516/43 830	0.93 (0.80 to 1.09)	23/2375	0.81 (0.47 to 1.41)
High	2225/169 656	1.18 (1.10 to 1.26)	588/46 489	0.95 (0.81 to 1.11)	31/2104	1.46 (0.87 to 2.45)
Very high	2527/149 571	1.33 (1.24 to 1.43)	402/27 981	0.91 (0.77 to 1.09)	39/4071	1.52 (0.90 to 2.57)
Per 0.1 increase§		1.16 (1.12 to 1.21)		0.93 (0.84 to 1.03)		1.39 (1.10 to 1.77)
Tumor histology	Adenocarcinoma cases (n = 3669)		Squamous cell carcinoma cases (n = 1667)		Small cell carcinoma cases (n = 1260)	
WHR						
Normal	590/187 535	1 (referent)	248/187 193	1 (referent)	184/187 129	1 (referent)
Moderate	1094/256 667	1.11 (1.00 to 1.23)	430/256 003	1.03 (0.88 to 1.21)	317/255 890	1.02 (0.85 to 1.22)
High	987/217 672	1.10 (0.99 to 1.23)	478/217 163	1.22 (1.04 to 1.43)	334/217 019	1.12 (0.93 to 1.35)
Very high	998/181 127	1.22 (1.09 to 1.36)	511/180 640	1.33 (1.12 to 1.57)	425/180 554	1.28 (1.05 to 1.54)
Per 0.1 increase§		1.10 (1.04 to 1.17)		1.21 (1.11 to 1.32)		1.16 (1.05 to 1.28)

*Cox regression analyses were carried out with stratification by cohort, year of enrollment (five-year intervals from <1985 to >2005), and year of birth (five-year intervals from <1925 to >1960), and adjustment for age, sex, race/ethnicity (white, black, Asian, or other), educational attainment (≤high school, vocational school or some college, college or graduate school), smoking history (never, former, or current use of cigarettes, cigars, or pipe), pack-years of cigarette smoking, age of smoking initiation, years since smoking cessation, family history of lung cancer (yes, no, or unknown), physical activity level (low, middle, or high, measured by metabolic equivalents or hours of exercise), alcohol consumption (none, moderate, or heavy [>14 g/d for women and >28 g/d for men]), BMI category, and, in women, menopausal status (pre or post). CI = confidence interval; HR = hazard ratio; WHR = waist-to-hip ratio.

†Normal, moderate, high, and very high WHR were defined as <0.90, 0.90–0.949, 0.95–0.99, or ≥1.00 for non-Asian men, <0.85, 0.85–0.899, 0.90–0.949, or ≥0.95 for Asian men, and <0.75, 0.75–0.799, 0.80–0.849, ≥0.85 for all women.

‡Potential interaction was evaluated via likelihood ratio test comparing models with and without the interaction terms. Potential heterogeneity was evaluated using Cochran's Q test. Two-sided $P_{interaction}$ values were .23 for WHR categories with sex, .06 with smoking status, and .02 with race/ethnicity. $P_{heterogeneity}$ between histological types was .39.

§To avoid influence of extreme values, participants at the top and bottom 1% of WHR were excluded from analysis.

abdominal and visceral fat (29,42). Our present findings and proposed explanations are supported by recent large-scale Mendelian randomization studies showing that genetically predicted BMI, WHR, and insulin resistance were statistically significantly associated with increased lung cancer risk, particularly for squamous cell and small cell lung cancer (43,44). Other factors that contribute to differential obesity phenotypes as well as lung cancer risk and subtypes, including genetic profile, estrogen level, and physical activity, may also underlie the obesity–lung cancer relationship (43–46). Future studies using advanced body composition measures (eg, imaging techniques) and molecular approaches (eg, metabolomics) may help elucidate underlying mechanisms. Meanwhile, appropriate prevention approaches, for example, lung cancer screening, may consider adding assessments of central obesity (especially for individuals who are normal or underweight) and obesity-related metabolic disorders to help identify high-risk individuals.

The present study has several strengths. The large sample size, long follow-up time, and individual-level data including detailed smoking information and tumor histology enable us to address potential confounding and reverse causation and to evaluate associations among never smokers and relatively rare lung cancer types. Moreover, our study included diverse populations from different regions and racial/ethnic groups. We found that the obesity–lung cancer associations appeared to differ by race, with blacks being most affected, no matter whether the cutoffs used were from project-wide WHO criteria, cohort-specific quintiles, or race-specific quintiles. This potential variation by race is plausible, given the racial differences in body composition, fat distribution, tobacco carcinogen metabolism, and lung cancer incidence rates (14–16).

The present study also has several limitations. First, because of its observational nature, our findings may be influenced by measurement errors in anthropometric variables and residual confounding in covariates such as smoking exposure. Second, anthropometrics and smoking information were collected at baseline and might have changed during follow-up. Third, statistical power for certain subgroup analyses are still inadequate, such as among blacks and for rare histological types. Also,

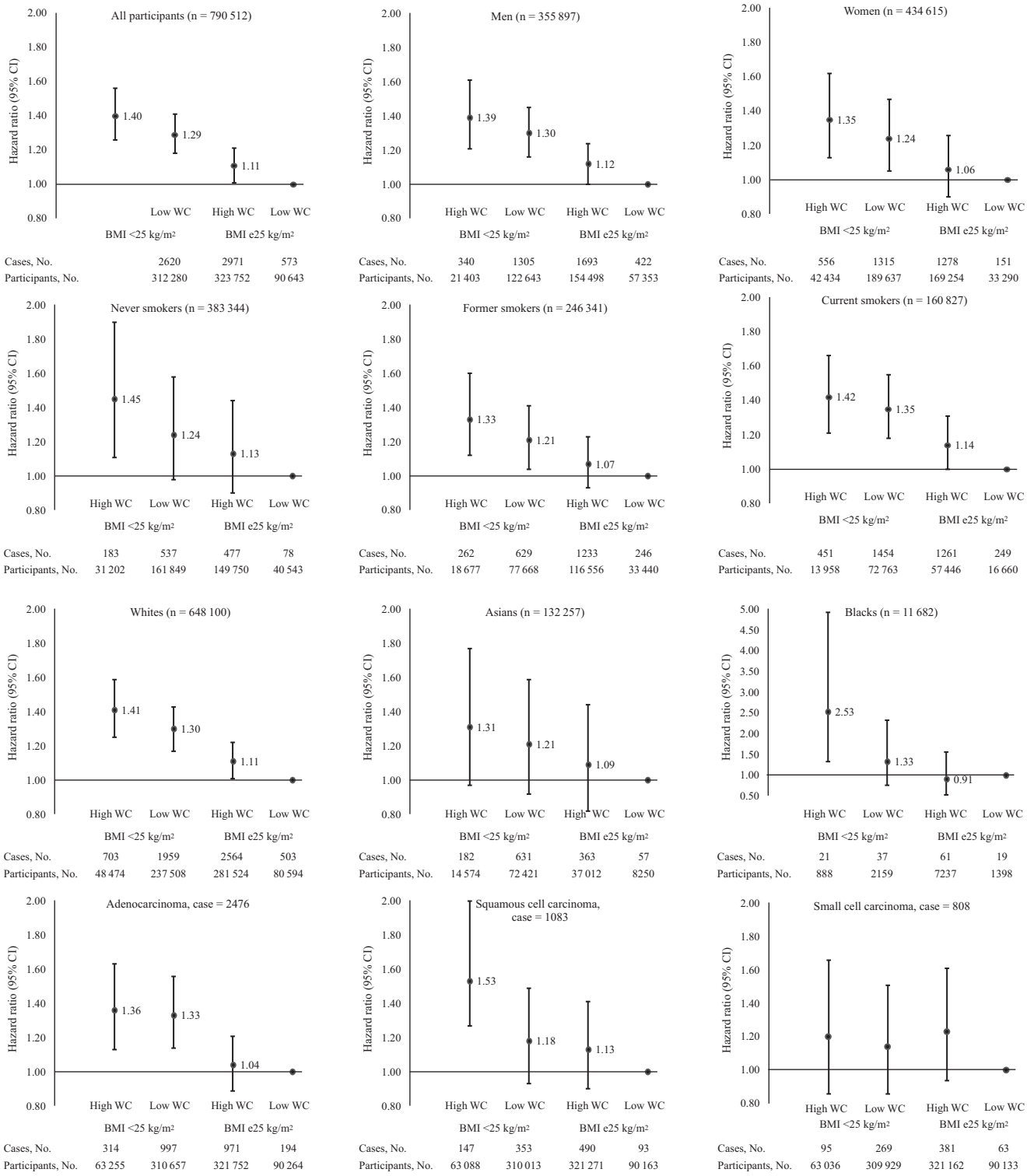

Figure 1. Joint effect of body mass index and waist circumference on lung cancer risk, excluding the first five years of follow-up, by sex, smoking status, race, and tumor histology. Cox regression analyses were carried out with stratification by cohort, year of enrollment (five-year intervals from <1985 to >2005), and year of birth (five-year intervals from <1925 to >1960), and adjustment for age, sex, race/ethnicity (white, black, Asian, or other), educational attainment (≤high school, vocational school or some college, college or graduate school), smoking history (never, former, or current use of cigarettes, cigars, or pipe), pack-years of cigarette smoking, age of smoking initiation, years since smoking cessation, family history of lung cancer (yes, no, or unknown), physical activity level (low, middle, or high, measured by metabolic equivalents or hours of exercise), alcohol consumption (none, moderate, or heavy [>14 g/d for women and >28 g/d for men]), and, in women, menopausal status (pre or post). High WC was defined as waist circumference ≥94 cm for non-Asian men, ≥90 cm for Asian men, and ≥80 cm for all women, according to World Health Organization classifications (high and very high levels as shown in Table 5). $P_{interaction}$ values were .95 with sex, .67 with smoking status, and .75 with race/ethnicity. $P_{heterogeneity}$ between histological types was .37. The entire follow-up time was included because of a small number of black participants. All statistical tests were two-sided. BMI = body mass index; CI = confidence interval; HR = hazard ratio; WC = waist circumference.

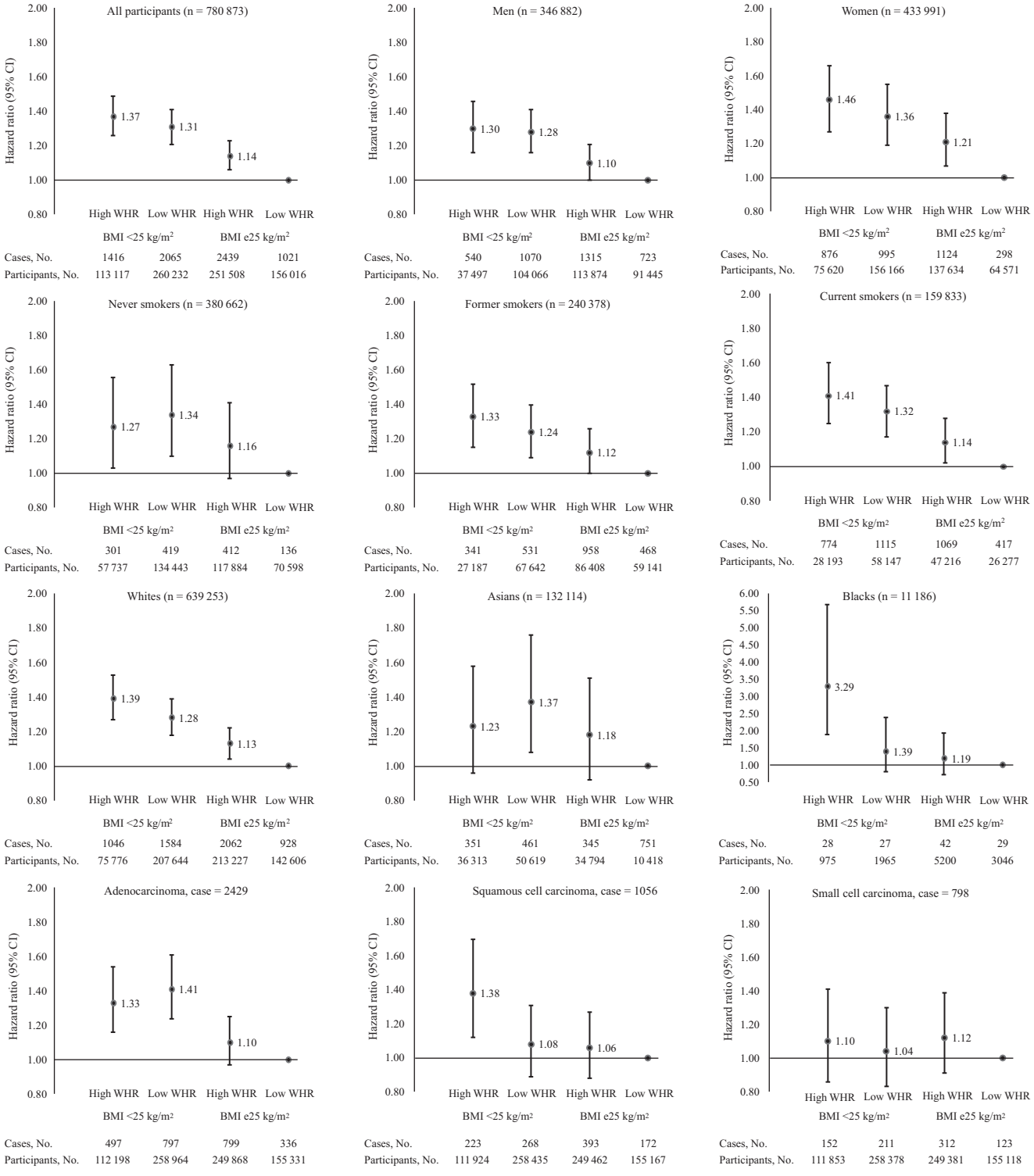

Figure 2. Joint effect of body mass index and waist-hip ratio on lung cancer risk, excluding the first five years of follow-up, by sex, smoking status, race, and tumor histology. Cox regression analyses were carried out with stratification by cohort, year of enrollment (five-year intervals from <1985 to >2005), and year of birth (five-year intervals from <1925 to >1960), and adjustment for age, sex, race/ethnicity (white, black, Asian, or other), educational attainment (≤high school, vocational school or some college, college or graduate school), smoking history (never, former, or current use of cigarettes, cigars, or pipe), pack-years of cigarette smoking, age of smoking initiation, years since smoking cessation, family history of lung cancer (yes, no, or unknown), physical activity level (low, middle, or high, measured by metabolic equivalents or hours of exercise), alcohol consumption (none, moderate, or heavy [>14 g/d for women and >28 g/d for men]), and, in women, menopausal status (pre or post). High WHR was defined as waist-hip ratio ≥0.95 for non-Asian men, ≥0.90 for Asian men, and ≥0.80 for all women, according to World Health Organization classifications (high and very high levels as shown in Table 6). $P_{interaction}$ values were .59 with sex, .59 with smoking status, and .09 with race/ethnicity. $P_{heterogeneity}$ between histological types was .88. Entire follow-up time was included because of a small number of black participants. All statistical tests were two-sided. BMI = body mass index; CI = confidence interval; HR = hazard ratio; WHR = waist-hip ratio.

because many subgroup analyses were conducted, some of the findings might be due to chance.

In conclusion, in this large pooled analysis, we found a general inverse association of BMI and positive associations of WC and WHR with lung cancer. The obesity–lung cancer association is not completely due to confounding by smoking or reverse causation and may vary by race/ethnicity and tumor histological type. In addition to smoking history and other established risk factors, a "low BMI–high WC/WHR" phenotype may help identify high-risk populations for lung cancer. Our findings also suggest the need for future research to examine the roles of body composition, fat distribution, and obesity-related metabolic disorders in the development of lung cancer.

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Notes

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Drs. Yu and Shu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Yu, Zheng, Shu. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: Yu, Shu. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Yu. Obtained funding: Takata, Shu. Administrative support and supervision: Shu.

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