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Association between adiposity measures and COPD risk in Chinese adults

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Take home message: Abdominal adiposity and underweight were risk factors for COPD in Chinese adults. Both BMI and measures of Abdominal adiposity should be considered in the prevention of COPD.

Abstract

Bodyweight and fat distribution may be related to Chronic obstructive pulmonary disease (COPD) risk. Limited prospective evidence linked COPD to abdominal adiposity. We investigated the association of body mass index (BMI) and measures of abdominal adiposity with COPD risk in a prospective cohort study.

The China Kadoorie Biobank (CKB) recruited participants aged 30-79 years from ten areas across China. Anthropometric indexes were objectively measured at the baseline survey during 2004-2008. After exclusion of participants with prevalent COPD and major chronic diseases, 452,259 participants were included and followed up through the end of 2016. We used Cox models to estimate adjusted hazard ratios relating adiposity to risk of COPD hospitalization or death.

Over an average of 10.1-year follow-up, 10,739 COPD hospitalization events and deaths were reported. Compared with normal BMI (BMI 18.5 to < 24.0 kg/m^2), underweight (BMI < 18.5 kg/m^2) individuals had increased risk of COPD, with adjusted HR (95% CI) to be 1.78 (1.66-1.89). Overweight (BMI 24.0 to < 28.0 kg/m^2) and obesity (BMI ≥ 28.0 kg/m^2) were not associated with an increased risk after adjustment for waist circumference. A higher waist circumference (≥ 85 cm for men and ≥ 80 cm for women) was positively associated with COPD risk after adjustment for BMI. Waist-to-hip ratio and waist-to-height ratio were also positively related to COPD risk.

Abdominal adiposity and underweight were risk factors for COPD in Chinese adults. Both BMI and measures of Abdominal adiposity should be considered in the prevention of COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a global health problem, causing about 3 million deaths every year[1]. In China, the prevalence of COPD is estimated to be 8.6% in adults over 20 years old, equivalent to 99.9 million prevalent cases[2]. Such a heavy disease burden has been a great concern. Identifying and modifying risk factors is essential for controlling the epidemic of COPD.

Adiposity is an established risk factor for a range of chronic diseases. Keeping a suitable body weight has been considered as a major part of healthy life style[3]. But the relationship between adiposity and COPD risk is not fully understood. Evidence from cross-sectional studies implied an inverse correlation between body mass index (BMI) and COPD prevalence[2, 4]. However, the observed relationship may not be causal as COPD patients often undergo weight loss and tend to be thinner than healthy people[5]. Prospective cohort studies could address reverse causality, while available prospective evidence is not sufficient. In addition to general adiposity measured by BMI, fat distribution may also be an important factor in the development of COPD. Abdominal adipose tissue contributes to systemic inflammation which is related to the pathogenesis of COPD. One large cohort study in the US found that obesity, in particular, abdominal adiposity measured by waist circumference was associated with an increased risk of COPD[6]. There are ethnic variations in body size and composition. Generally, Chinese people have lower BMI and a higher percentage of body fat than Caucasians[7]. Whether the association between adiposity and COPD holds in the Chinese population is unclear.

The objective of this study is to examine the association of general and abdominal adiposity measures with risk of COPD hospitalization or death in a population-based prospective cohort, the China Kadoorie Biobank (CKB) study.

Methods

Study population

Details of the CKB study have been described previously[8, 9]. Adults aged 30-79 years were recruited from 10 regions across China, including five urban and five rural regions (Figure S1). The CKB study is not designed to be representative of Chinese population, and the cohort was not a random sample. However, the study selected 10 geographically diverse regions to represent major regional differences in disease patterns, lifestyles, and economic levels throughout China. In each administrative unit, all men and women who were permanently resident and without a major disability were identified and invited to participate. The participation rate was about 30%. A total of 512,715 participants completed the baseline survey. The sample size of 0.5 million was determined to achieve acceptable statistical power to detect the complex interplay between environmental and genetic factors of common chronic diseases. The CKB study was approved by the Ethical Committee of the Chinese Center for Disease Control and Prevention (Beijing, China) and the Oxford Tropical Research Ethics Committee, University of Oxford (UK). Signed informed consent was obtained from all participants.

Assessment of exposure and covariates

Anthropometric measurements were collected by trained staff according to standard procedures[10] at the baseline survey between June 2004 and July 2008. Standing height was measured without shoes, to the nearest 0.1 cm, using stadiometer. Weight was measured without shoes but in light clothing, to the nearest 0.1 kg, using the TBF-300GS Body Composition Analyser (Tanita inc, Tokyo, Japan). The weight of clothing was estimated and subtracted according to the season. Waist and hip circumference were measured to the nearest 0.1 cm using soft tape. The reliability of anthropometric measurements was evaluated in a re-survey among 5% of randomly chosen participants in 2008. The correlation coefficients between baseline and re-survey measures were quite high for height (0.99), weight (0.96), waist circumference (0.84), and hip circumference (0.82). BMI was calculated as weight (kg) divided by the square of height (m^2). Waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) were calculated as waist circumference divided by hip circumference and height, respectively.

At the baseline survey, information on covariates was collected using an interviewer-administered questionnaire, including socio-demographic factors (age, sex, marital status, and highest education), lifestyle (smoking, passive smoking, alcohol drinking, physical activity, diet, and household air pollution), and medical history (respiratory symptoms, asthma, tuberculosis). Passive smoking was evaluated by asking if participants had lived with smoker in the same house and the duration of exposure. Household air pollution was evaluated by solid fuel use for cooking and heating in the house. A food frequency questionnaire comprising 12 major food groups was used to assess diet. Daily physical activity level was assessed by calculating the Metabolic Equivalent Task-hours (MET-h). Pre-bronchodilator FEV_1 and FVC were measured by trained technicians following recommended procedures[11].

Assessment of outcome

Participants were followed up until the date of COPD (ICD-10: J41-J44) incidence, death, loss to follow-up, or December 31, 2016, whichever came first. The vital status and causes of death were obtained through official residential records and death certificates. Information on COPD morbidity was also collected through electronic linkage with national health insurance (HI) system, which was established recently in all study regions and contained detail hospitalization information. Incident cases from HI database were hospitalization events, without including diagnoses made in an outpatient setting. Participants may be hospitalized and receive a COPD diagnosis due to COPD exacerbation, severe respiratory symptoms, or comorbidities. Linkage with HI database had been achieved for 98% of cohort participants. Active follow-up was conducted annually for participants who failed to be linked to the local HI database. In active follow-up, the interviewer asked participants if they had received a diagnosis of COPD by a physician during the past year. Less than 1% (4,875) of participants were lost to follow-up. To evaluate the validity of COPD diagnosis in CKB study, 1,069 randomly selected cases were adjudicated. A diagnosis of COPD was confirmed in 85% reported cases[12].

Statistical analyses

We excluded participants who had been diagnosed with chronic bronchitis or emphysema by a physician (n=13,288), or those who had airflow obstruction defined as the ratio of forced expiratory volume in one second over forced vital capacity (FEV1/FVC) <0.7 (n=27,483). We also excluded participants with prevalent cancer (n=2,578), coronary heart disease (n=15,472), asthma (n=2,806), or tuberculosis (n=7,659), as these diseases may cause significant weight change. Two participants were additionally excluded because of missing BMI. Finally, 452,259 participants were included in the present analysis.

General adiposity was defined based on BMI using cut-off points according to the guidelines for prevention and control of overweight and obesity in Chinese adults[13,14]. Participants were categorized into four groups: underweight (<18.5 kg/m^2), normal (18.5 to <24.0 kg/m^2), overweight (24.0 to <28.0 kg/m^2), and obesity (≥28.0 kg/m^2). Abdominal adiposity was evaluated with waist circumference, WHR, and WHtR, according to previously recommended cut-off points[13, 15]. We also used restricted cubic splines with four knots at the 5th, 35th, 65th, and 95th percentiles of adiposity measures distribution to examine the non-linear relationship.

Cox regression model was used to calculate the hazard ratios (HRs) and 95% confidence intervals (95% CI) for the association between adiposity measures and risk of COPD hospitalization or death, with age as the time scale, stratified jointly by regions and 5-year birth cohorts. Potential confounders were adjusted for in the multivariate Cox model: sex, education, marital status, smoking status, passive smoking, cooking and heating fuel type, alcohol drinking, physical activity (MET-h/day), intake frequencies of red meat, fresh fruits, and vegetables, and respiratory symptoms. These covariates were selected based on prior knowledge, including social-demographic variables, established risk factors for COPD, and health-related lifestyles which may influence body weight. We used Schoenfeld residuals to check the proportional hazards assumption for all models and found no violation.

We also examined the association in various subgroups defined by baseline characteristics: sex (male, female), area (urban, rural), age (<50, 50-59, ≥60), education level (primary school or lower, middle/high school, college or higher), smoking status (non-smoker, current smoker), menopause (no, yes), and physical activity (three groups defined by gender-specific tertiles). Joint analysis of general and abdominal adiposity measures was performed. We conducted the following sensitivity analyses to test the robustness of our results: excluding participants who developed COPD in the first three years of follow-up; restricting the analysis in never smokers; using the lower limit of normal (LLN) definition to exclude participants with airflow obstruction at baseline; excluding participants with diabetes at baseline. All analyses were performed using Stata (version 14.0, StataCorp, College Station, Texas). The significance level was set at 0.05.

Results

Among the 452,259 participants, 182,209 (40.3%) were male and 255,031 (56.4%) were from rural areas. The mean age at baseline was 51.1 (SD 10.4) years. The overall mean BMI was 23.7 (SD 3.3) kg/m^2, with 3.9% being underweight (BMI < 18.5 kg/m^2), 33.5% being overweight (BMI 24.0 to <28.0 kg/m^2), and 10.5% being obese (BMI ≥28.0 kg/m^2). The overall mean waist circumference was 80.3 (SD 9.6) cm, with 41.9% being abdominal obese (waist circumference ≥ 85 cm for men; waist circumference ≥ 80 cm for women). Participants with higher BMI were more likely to be urban residents, to consume fresh fruits, vegetables, and red meat daily, and were less likely to be current smokers (P < 0.001). Compared with participants with normal BMI, those with lower or higher BMI were more likely to be older, female, physically inactive, and have respiratory symptoms at baseline (P < 0.001). Similar results were observed for abdominal adiposity categories defined by waist circumference, WHR, and WHtR (Table1, Table S1).

General adiposity and COPD

During a median follow-up of 10.1 years (interquartile range 2.2-11.1 years), we documented 10,739 COPD hospitalization events and deaths. The overall incidence rate for hospitalization or death from COPD was 2.40/1,000 person-years. Individuals with a BMI of less than 18.5 kg/m^2 had a higher incidence rate (7.08/1,000 person-years). After adjusting for major covariates, underweight and obese participants had HRs (95% CI) of 1.75 (1.64-1.86) and 1.10 (1.02-1.19) respectively as compared with participants with normal BMI. The association between obesity and COPD disappeared after additional adjustment for waist circumference, while underweight remained a statistically significant risk factor, with HR (95% CI) being 1.78 (1.66-1.89).

We observed that the association between BMI and COPD differed by gender ($P_{interaction}$< 0.001), and the stratified results were also presented (Table 2). BMI was inversely associated with COPD risk in men. Overweight and obesity appeared to be protective factors, with adjusted HRs (95% CI) being 0.84 (0.77-0.90) and 0.76 (0.65-0.90). The inverse association was weaker in women than in men, and no statistically significant association was found between obesity and COPD in women. We also used restricted cubic splines to investigate the non-linear relationship between BMI and COPD. In men, COPD risk decreased with higher BMI and leveled off at a BMI of 23 kg/m^2. In women, the lowest risk of COPD was at BMI around 23-24 kg/m^2, and BMI higher than 24 kg/m^2 appeared to be associated with increased risk of COPD (Figure 1). The association between BMI and COPD risk was modified by baseline age, area, smoking status, and level of physical activity (Table S2).

Abdominal adiposity and COPD

Overall, participants in the lowest waist circumference group had the highest crude incidence rate for hospitalization or death from COPD (4.78/1,000 person-years). After adjustment for covariates and BMI, abdominal adiposity was associated with COPD, and the risk increased with higher waist circumference. The adjusted HR (95% CI) for the highest waist circumference group (≥ 95 cm for men; ≥ 90 cm for women) was 1.57 (1.43-1.73) compared with normal group (waist circumference 70 to < 85 cm for men; 65 to < 80 cm for women) (Table 3). The positive trend for abdominal adiposity and COPD was similar in men and women, while the association between lower waist circumference and COPD was limited to women. Based on models with spline terms, waist circumference was positively associated with COPD in men, and those with waist circumference lower than 75 cm had the lowest risk. In women, waist circumference and COPD showed a U-shape relationship, with the lowest risk at waist circumference around 72-75 cm (Figure 1). The association between waist circumference and COPD risk was modified by baseline age, area, and level of physical activity (Table S3). Consistent results were observed when using WHR and WHtR as measures of abdominal adiposity (Table S4).

Joint analysis of general and abdominal adiposity

No statistically significant interaction was found between waist circumference and BMI categories on COPD risk ($P_{\text{interaction}}$= 0.703). Within each BMI category, the risk of COPD increased with waist circumference. Overweight participants with low waist circumference (< 85 cm for men; < 80 cm for women) had the lowest risk of COPD (HR: 0.87, 95% CI: 0.80-0.95) (Table 4). WHtR was also positively associated with COPD, and no significant heterogeneity between BMI categories was found ($P_{\text{interaction}}$= 0.462). The association of WHR with COPD was not consistent across BMI categories ($P_{\text{interaction}}$= 0.017), with a negative trend observed in the underweight group (BMI < 18.5 kg/m^2).

Sensitivity analysis

In the sensitivity analyses, the major results remained largely unchanged with excluding participants who developed COPD in the first three of follow-up (n= 1,849), excluding participants with diabetes at baseline (n= 28,214), or using LLN definition for airflow obstruction. Among never smokers (n= 284,259), the HR (95% CI) of underweight group (BMI < 18.5 kg/m^2) was attenuated to 1.64 (95% CI: 1.48-1.81). The risk estimates for abdominal adiposity measures were not substantially altered when restricting the analysis to never smokers (Table S5).

Discussion

In this population-based cohort study with ten years of follow-up, abdominal adiposity defined by waist circumference was associated with a higher risk of COPD hospitalization or death among Chinese adults. The association was independent of general adiposity defined by BMI. WHR and WHtR were also positively related to the risk of COPD. Low BMI (< 18.5

kg/m^2) appeared to be a significant risk factor for COPD, while overweight (BMI 24.0 to <28.0 kg/m^2) and obesity (BMI ≥28.0 kg/m^2) did not appear to increase COPD risk after adjustment for waist circumference. In men, being overweight or obese was associated with a lower risk of COPD.

Compared with general adiposity, abdominal adiposity which reflects fat distribution may be more relevant to COPD risk. Waist circumference is a widely used measurement of abdominal adiposity in epidemiologic studies. Many studies have found that high waist circumference was associated with reduced lung function[16-19]. In the NIH-AARP Diet and Health Study, waist circumference showed a positive association with the risk of COPD after adjustment for BMI[6]. Similar results were observed in our Chinese population. We also evaluated the joint effect of BMI and waist circumference on risk of COPD hospitalization or death and found no statistically significant interaction. High waist circumference was consistently associated with a higher risk across BMI categories. Overweight people with lower waist circumference were at the lowest risk of COPD as they had higher muscular mass and lower abdominal fat mass. Furthermore, other measures of abdominal adiposity, including WHR and WHtR, were found to be positively associated with COPD in the present study. The possible mechanism underlying the association between abdominal adiposity and COPD is related to inflammation. It has been well known that inflammation plays a crucial role in COPD. As an active endocrine organ, adipose tissue is a source of proinflammatory mediators. The increased inflammatory mediators may attract inflammatory cells and amplify the inflammatory process, resulting in structural changes of small airways[20]. Among never smokers, COPD risk also increased with higher waist circumference in our study, suggesting that abdominal adiposity may be an important risk factor in never smokers. Reducing abdominal adiposity should be recommended to prevent COPD regardless of smoking status.

Previous literature consistently showed that participants with lower BMI had lower lung function and a higher risk of COPD[21-23]. In line with previous data, our prospective study found that underweight individuals had an increased risk of COPD. In sensitivity analyses, we excluded incident cases in the first two years of follow-up to address reverse causation. We also restricted the analysis to never smokers, as smoking may be a confounder between lower BMI and a higher risk of COPD[24]. Possible explanations include malnutrition, weak resistance against respiratory infection, and low muscularity in underweight people[25-27]. The increased risk of COPD among underweight people may also be related to Sarcopenia, which is frequently observed in COPD patients[28].

Existing study results for the association of general adiposity with COPD are somewhat inconsistent. A meta-analysis found that measures of lung function decreased among obese adults[29]. However, high BMI did not appear to increase COPD risk[4, 21]. In a recent large cross-sectional study in China[2], compared with healthy weight (BMI 18.5-24.9 kg/m^2), overweight and obesity (BMI ≥ 25 kg/m^2) was associated with a 25% decreased the risk of COPD prevalence (OR=0.75, 95% CI: 0.62-0.92). In our analysis, being overweight (BMI 24.0 to < 28.0) or obese (BMI ≥28.0 kg/m^2) was also shown to be a protective factor in men after adjustment for waist circumference. To interpret this result correctly, it is important to understand the meaning of our statistical model. When holding abdominal adiposity constant, BMI primarily reflects lean body mass instead of fatness[30]. Skeleton muscle, a major part of lean body tissues, is positively associated with lung function[27]. Therefore, the lower risk in the overweight group is likely due to the protective effect of muscularity. Similarly, previous studies showed that overweight and obese patients with COPD have a lower mortality rate, which is known as "obesity paradox"[31]. Muscular mass could be taken into account to further elucidate the mechanism in the future. We also observed that being overweight was associated with a significantly lower risk of COPD only among those with higher level of physical activity, indicating that such protective effect could be related to physical activity. Exercising and increasing muscle mass may help prevent COPD.

To the best of our knowledge, this is the first large cohort study to investigate the association of both general and abdominal adiposity with risk of COPD hospitalization or death in China. Various anthropometric indexes were objectively measured in the baseline study, allowing us to evaluate the independent effect of general and abdominal adiposity on COPD. Our main strengths include the prospective design, large sample size, and stringent quality control process. We made efforts to reduce bias from reverse causation and confounding by smoking in data analysis. The results of sensitivity analyses indicated that our major findings were reliable.

There are also limitations in the present study. The first one is the outcome misclassification. Spirometry was not performed on all participants during follow-up, and COPD cases were identified through HI database and death certificates. COPD is often under-diagnosed in China[32], and the under-diagnosis may be more severe among obese individuals[33]. Such misclassification would result in an underestimate of relative risk in obese individuals. Another concern is the low utility of spirometry among COPD cases (13.9%)[12]. Similarlly, only 12.0% of people with COPD reported a previous pulmonary function test in a recent nationally representative survey[2]. However, most COPD diagnoses (85%) in our study were supported by different sources of evidence including respiratory symptoms, risk factors, and radiological examinations[12]. Second, despite excluding participants with specific pre-existing diseases or those who developed COPD in the first three years of follow-up, reverse causation could still not be entirely eliminated due to subclinical conditions. Third, many covariates were self-reported, which may have measurement error. However, the measurements of important confounders such as smoking showed good quality in reproducibility.

In summary, abdominal adiposity is a predictor of COPD risk independent of general adiposity. For people with any level of BMI, maintaining a proper waist circumference would help prevent COPD if the association is confirmed to be causal. Low BMI (< 18.5 kg/m^2) is also a significant risk factor for COPD. Therefore, maintaining a healthy BMI (i.e. between 18.5 and 24 kg/m^2) and avoid abdominal adiposity should be both considered in the management of body weight to reduce the future risk of COPD. Our data would provide useful information for determining optimal BMI and waist circumference cut-off points among Chinese people.

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Figure legend

Figure 1. Association of body-mass index and waist circumference with COPD risk for men and women

BMI, body mass index (kg/m^2); WC, waist circumference (cm)

BMI or WC was included as restricted cubic spline terms in the Cox model, using four knots at the 5th, 35th, 65th, and 95th percentiles. Covariate adjustment was based on model 3. The reference BMI was 21 kg/m^2. The reference WC was 77 cm for men and 72 cm for women. P values for non-linearity were all < 0.0001.

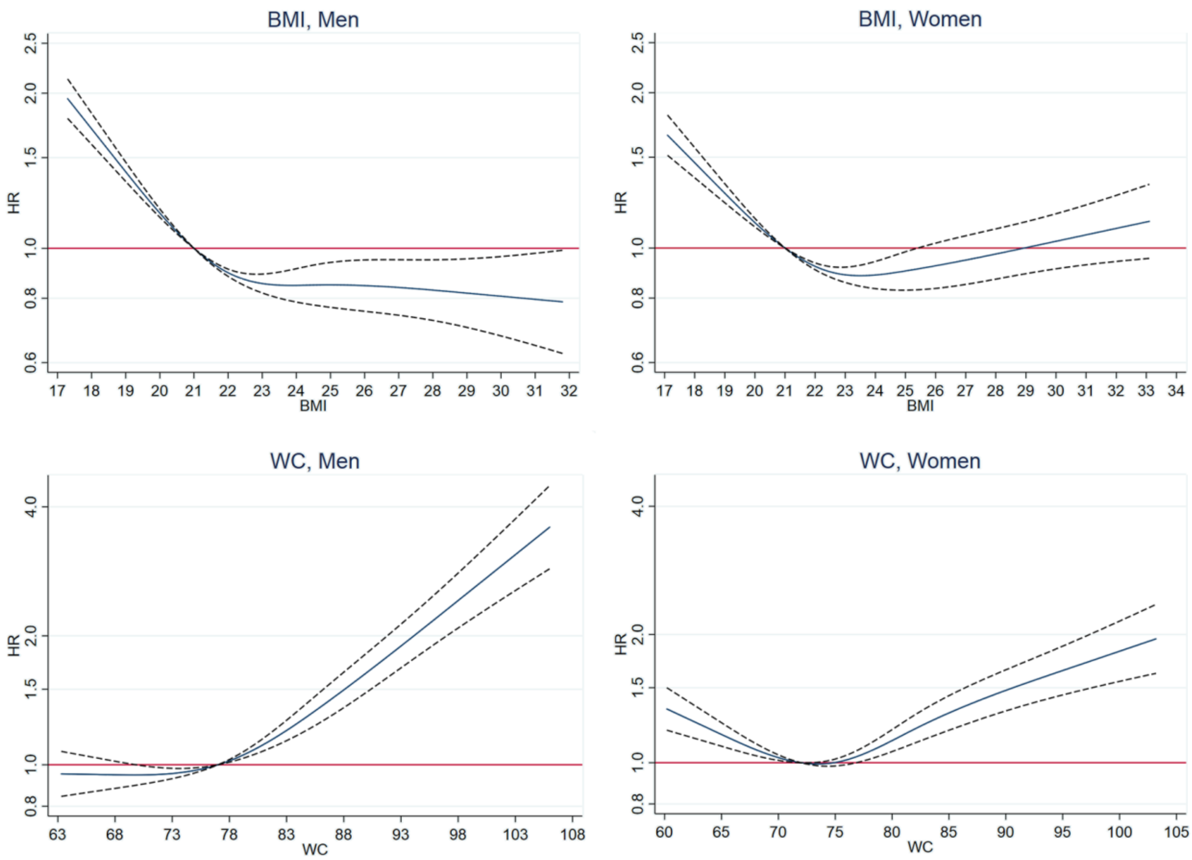
BMI, Men
BMI, Women
WC, Men
WC, Women
HR
BMI
WC
2.5
2.0
1.5
1.0
0.8
0.6
4.0
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
63 68 73 78 83 88 93 98 103 108
60 65 70 75 80 85 90 95 100 105

Table 1. Baseline characteristics of participants by baseline body-mass index and waist circumference (n=452 259)

	BMI (kg/m^2)				Waist circumference (cm)	
	< 18.5	18.5 to < 24.0	24.0 to < 28.0	≥ 28.0	< 85 (male) < 80 (female)	≥ 85 (male) ≥ 80
Number of participants	17,57	235,379	151,649	47,65	262,902	189,357
Age (years)	53.8	50.7	51.3	51.9	49.3	52.8
Female (%)	61.0	58.1	60.0	66.1	57.1	63.3
Urban (%)	31.3	38.3	49.7	55.1	38.3	50.9
Married (%)	88.6	90.6	92.3	92.1	90.7	91.9
Primary school or lower	51.5	49.4	49.1	51.9	49.5	49.8
Current smoker (%)	32.4	27.9	24.0	23.0	27.4	24.7
Passive smoker (%)	45.7	44.7	44.4	44.9	44.8	44.4
Cooking with solid fuel	40.2	36.9	35.4	35.1	37.3	35.0
Heating with solid fuel	38.5	37.3	36.9	37.4	37.3	37.1
Drinking weekly (%)	13.9	15.1	14.8	14.5	14.6	15.3
Consuming fruits daily	14.9	18.2	19.0	19.3	18.2	19.0
Consuming fresh	93.1	94.4	95.1	95.1	94.3	95.1
Consuming meat daily	25.8	28.3	30.7	31.4	28.1	31.1
Physical activity (Met-	21.5	22.2	21.3	20.1	22.2	20.8
Respiratory symptoms	13.0	11.3	12.6	16.1	11.5	13.4

Note: BMI, body mass index

Linear (for continuous variable) or logistic (for categorical variables) models were used to calculate predictive margins adjusting for age, sex, and region.

[a] Hving respiratory symptoms was defined as the presence of any one of the four symptoms: 1) usually become short of breath when walking on level ground, 2) usually slow down due to chest discomfort when walking on level ground, 3) cough frequently during the past 12 months, and 4) cough up sputum after getting up in the morning during the past 12 months.

Table 2. Association between baseline body-mass index and risk of COPD

	BMI (kg/m²)			
	< 18.5	18.5 to < 24.0	24.0 to < 28.0	≥ 28.0
Total (n=452,259)				
Case	1,173	5,809	2,859	898
Rate (per 1000 person-years)	7.08	2.49	1.89	1.90
HR (95% CI) model 1	1.86 (1.75-1.99)	1.00	0.95 (0.91-1.00)	1.12 (1.04-1.20)
HR (95% CI) model 2	1.75 (1.64-1.86)	1.00	0.97 (0.93-1.02)	1.10 (1.02-1.19)
HR (95% CI) model 3	1.78 (1.66-1.89)	1.00	0.89 (0.84-0.95)	0.95 (0.87-1.05)
Male (n=182,209)				
Case	651	3,099	1,208	255
Rate (per 1000 person-years)	10.46	3.26	2.01	1.56
HR (95% CI) model 1	2.05 (1.88-2.23)	1.00	0.86 (0.80-0.92)	0.85 (0.75-0.97)
HR (95% CI) model 2	1.90 (1.74-2.07)	1.00	0.89 (0.83-0.95)	0.88 (0.77-1.00)
HR (95% CI) model 3	1.91 (1.75-2.08)	1.00	0.84 (0.77-0.90)	0.76 (0.65-0.90)
Female (n=270,050)				
Case	522	2,710	1,651	643
Rate (per 1000 person-years)	5.05	1.96	1.82	2.08
HR (95% CI) model 1	1.67 (1.52-1.84)	1.00	1.02 (0.96-1.09)	1.27 (1.16-1.39)
HR (95% CI) model 2	1.59 (1.44-1.75)	1.00	1.02 (0.96-1.09)	1.23 (1.12-1.34)
HR (95% CI) model 3	1.64 (1.49-1.81)	1.00	0.92 (0.85-1.00)	1.05 (0.93-1.18)

Note: BMI, body mass index

Models were adjusted for: model 1: sex (only in total population); Model 2: additionally included education (none or primary school, middle or high school, college or university), marital status (married, widowed, divorced or separated, never married), smoking (never or occasional, former and having quitted <5, or ≥5 years, current smoking <15, 15 to 24, or ≥25 cigarettes/day), passive smoking (never lived with smoker, lived with smoker for <20 years, lived with smoker for ≥20 years and exposure < 20 hours/week, lived with smoker for ≥20 years and exposure ≥20 hours/week), cooking and heating fuel type (coal, wood/charcoal, cleaner fuel, other fuels, no cooking/heating), alcohol drinking (non-drinker, occasional drinker, former drinker, regular drinker), intake frequencies of red meat, fresh fruits, and vegetables (daily, 4-6 days/week, 1-3 days/week, monthly, rarely or never), physical activity (MET h/day), and respiratory symptoms (presence or absence); model3: additionally adjusted for waist circumference. *P* value for interaction between sex and BMI < 0.001.

Table 3. Association between baseline waist circumference and the risk of COPD

	Waist circumference (cm)				
	< 70 (male) < 65 (female)	70 to < 85 (male) 65 to < 80 (female)	85 to < 90 (male) 80 to < 85 (female)	90 to < 95 (male) 85 to < 90 (female)	≥ 95 (male) ≥ 90 (female)
Total (n=452,259)					
Case	1,478	5,254	1,639	1,164	1,204
Rate (per 1000 person-years)	4.78	2.27	2.05	2.14	2.35
HR (95% CI) model 1	1.44 (1.36-1.52)	1.00	0.99 (0.93-1.04)	1.05 (0.98-1.12)	1.14 (1.07-1.22)
HR (95% CI) model 2	1.35 (1.28-1.44)	1.00	1.00 (0.94-1.06)	1.05 (0.99-1.12)	1.11 (1.04-1.19)
HR (95% CI) model 3	1.16 (1.09-1.24)	1.00	1.15 (1.08-1.23)	1.31 (1.21-1.41)	1.57 (1.43-1.73)
Male (n=182,209)					
Case	1,004	2,794	624	416	375
Rate (per 1000 person-years)	6.10	3.01	2.11	1.97	2.09
HR (95% CI) model 1	1.40 (1.30-1.51)	1.00	0.88 (0.80-0.96)	0.90 (0.81-1.00)	1.02 (0.92-1.15)
HR (95% CI) model 2	1.33 (1.23-1.43)	1.00	0.90 (0.82-0.98)	0.93 (0.83-1.03)	1.03 (0.92-1.16)
HR (95% CI) model 3	1.02 (0.94-1.12)	1.00	1.17 (1.06-1.30)	1.39 (1.23-1.58)	1.90 (1.64-2.21)
Female (n=270,050)					
Case	474	2,460	1,015	748	829
Rate (per 1000 person-years)	3.28	1.77	2.02	2.24	2.49
HR (95% CI) model 1	1.45 (1.31-1.60)	1.00	1.07 (0.99-1.15)	1.16 (1.07-1.26)	1.22 (1.13-1.33)
HR (95% CI) model 2	1.39 (1.26-1.53)	1.00	1.07 (1.00-1.15)	1.15 (1.06-1.25)	1.18 (1.09-1.28)
HR (95% CI) model 3	1.28 (1.15-1.42)	1.00	1.15 (1.06-1.25)	1.28 (1.16-1.41)	1.40 (1.24-1.58)

Note: Models were adjusted for: model 1: sex (only in total population); Model 2: additionally included education (none or primary school, middle or high school, college or university), marital status (married, widowed, divorced or separated, never married), smoking (never or occasional, former and having quitted <5, or ≥5 years, current smoking <15, 15 to 24, or ≥25 cigarettes/day), passive smoking (never lived with smoker, lived with smoker for <20 years, lived with smoker for ≥20 years and exposure < 20 hours/week, lived with smoker for ≥20 years and exposure ≥20 hours/week), cooking and heating fuel type (coal, wood/charcoal, cleaner fuel, other fuels, no cooking/heating), alcohol drinking (non-drinker, occasional drinker, former drinker, regular drinker), intake frequencies of red meat, fresh fruits, and vegetables (daily, 4-6 days/week, 1-3 days/week, monthly, rarely or never), physical activity (MET h/day), and respiratory symptoms (presence or absence); model3: additionally adjusted for BMI. *P* value for interaction between sex and waist circumference = 0.0821 (model 3).

Table 4. Joint association of BMI and abdominal adiposity measures with COPD risk (HR 95%CI)

Abdominal adiposity	BMI (kg/m^2)				P for interaction
	< 18.5	18.5 to < 24.0	24.0 to < 28.0	≥ 28.0	
Waist circumference (cm)					0.703
< 85 (male) < 80 (female)	1.77 (1.66-1.89)	1.00	0.87 (0.80-0.95)	1.04 (0.59-1.83)	
85 to < 90 (male) 80 to < 85 (female)	1.91 (0.85-4.25)	1.08 (1.00-1.17)	0.95 (0.88-1.02)	1.18 (0.92-1.50)	
≥ 90 (male) ≥ 85 (female)	2.14 (0.53-8.57)	1.09 (0.95-1.26)	1.08 (1.01-1.15)	1.12 (1.04-1.21)	
WHR					0.017
< 0.9 (male) < 0.8 (female)	1.87 (1.72-2.02)	1.00	0.81 (0.70-0.94)	0.78 (0.46-1.32)	
0.9 to < 0.95 (male) 0.8 to < 0.85 (female)	1.75 (1.51-2.01)	1.01 (0.94-1.08)	0.90 (0.82-0.99)	1.01 (0.81-1.26)	
≥ 0.95 (male) ≥ 0.85 (female)	1.58 (1.30-1.93)	1.09 (1.02-1.17)	1.06 (0.99-1.13)	1.17 (1.07-1.28)	
WHtR					0.462
< 0.5	1.79 (1.67-1.92)	1.00	0.87 (0.76-0.99)	0.40 (0.06-2.84)	
≥ 0.5	1.78 (1.18-2.69)	1.07 (1.01-1.13)	1.01 (0.96-1.06)	1.13 (1.05-1.22)	

Note: BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio

HRs were estimated by joint categorization of BMI and each measure of abdominal adiposity (waist circumference, WHR, and WHtR). Covariate adjustment was based on model 2. P values for interaction were calculated by likelihood ratio test comparing models with and without a product term of BMI and abdominal adiposity measures.

Association between adiposity measures and COPD risk in Chinese adults

Online Data Supplement

Jiachen Li, Lu Zhu, Yuxia Wei, Jun Lv, Yu Guo, Zheng Bian, Huaidong Du, Ling Yang, Yiping Chen, Yonglin Zhou, Ruqin Gao, Junshi Chen, Zhengming Chen, Weihua Cao, Canqing Yu, Liming Li, on behalf of the China Kadoorie Biobank Collaborative Group

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Figure S1. Geographic locations of the CKB study regions

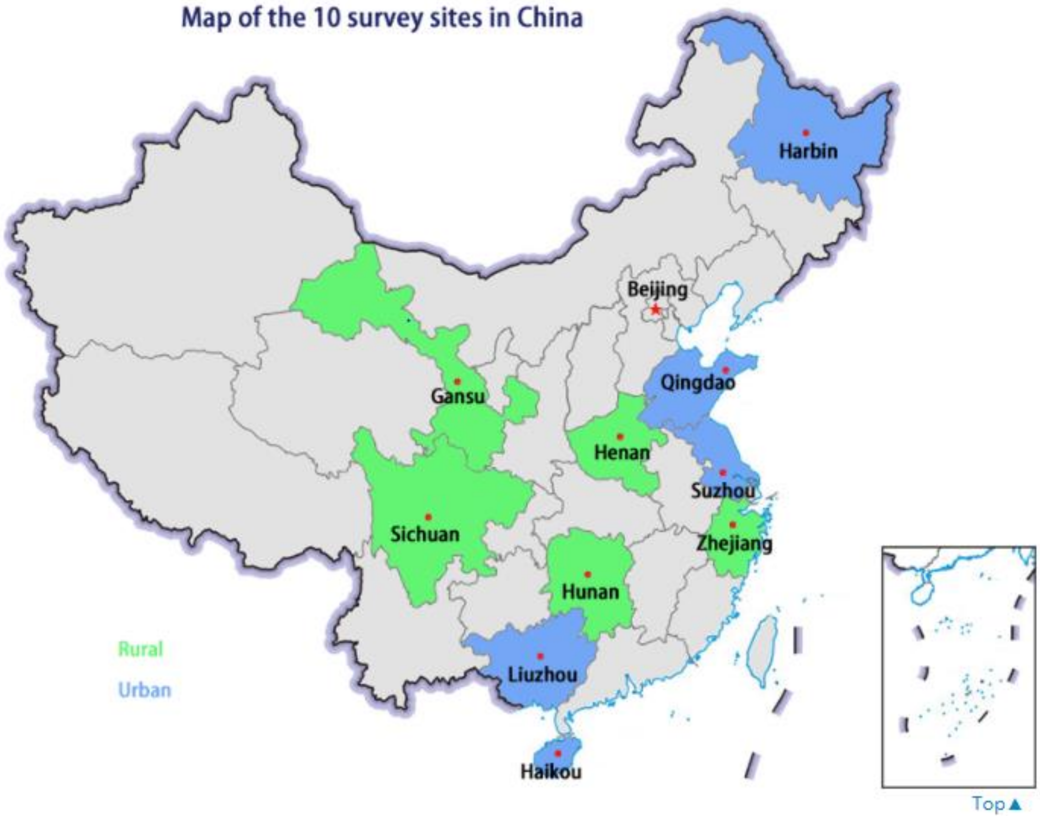

Table S1. Baseline characteristics of participants by baseline waist-to-hip ratio and waist-to-height ratio (n=452,259)

	WHR		WHtR	
	< 0.9 (male) < 0.8 (female)	≥ 0.9 (male) ≥ 0.8 (female)	< 0.5	≥ 0.5
Number of participants	124,096	328,163	217,831	234,428
Age (years)	49.5	51.8	49.4	52.7
Female (%)	33.3	69.7	54.9	64.1
Urban (%)	45.7	42.8	39.5	47.4
Married (%)	89.6	91.7	90.3	91.9
Primary school or lower (%)	49.3	49.8	49.0	50.2
Current smoker (%)	27.3	25.6	27.9	24.6
Passive smoker (%)	44.8	44.6	44.7	44.6
Cooking with solid fuel (%)	37.8	36.0	37.1	35.7
Heating with solid fuel (%)	37.0	37.3	37.2	37.2
Drinking weekly (%)	13.7	15.7	14.6	15.2
Consuming fruits daily (%)	18.8	18.4	18.6	18.5
Consuming fresh vegetables daily (%)	94.5	94.7	94.4	94.9
Consuming meat daily (%)	27.6	30.2	28.1	30.5
Physical activity (Met-h/d)	22.5	21.3	22.3	21.1
Respiratory symptoms (%)	11.4	12.7	11.4	13.1

Note: WHR, waist-to-hip ratio; WHtR, waist-to-height ratio

Predictive margins adjusting for age, sex and region were presented.

Table S2. Subgroup analysis for BMI and COPD according to age, area, education level, smoking status, physical activity, and menopause status

	Number	BMI (kg/m2)				$P_{interaction}$
		< 18.5	18.5 to < 24.0	24.0 to < 28.0	≥ 28.0	
Age (years)						0.0225
<50	217,796	1.40 (1.12-1.76)	1.00	0.88 (0.76-1.01)	0.95 (0.74-1.21)	
50-59	139,336	2.04 (1.80-2.32)	1.00	0.97 (0.87-1.07)	1.05 (0.89-1.24)	
≥60	95,127	1.73 (1.60-1.88)	1.00	0.84 (0.77-0.91)	0.89 (0.78-1.01)	
Area						0.0004
Urban	197,228	1.83 (1.55-2.16)	1.00	0.78 (0.69-0.88)	0.85 (0.71-1.01)	
Rural	255,031	1.77 (1.65-1.90)	1.00	0.93 (0.87-0.99)	1.01 (0.90-1.13)	
Education						0.2853
Primary school or lower	224,483	1.79 (1.67-1.92)	1.00	0.90 (0.84-0.96)	0.97 (0.87-1.08)	
Middle/high School	201,723	1.73 (1.46-2.04)	1.00	0.85 (0.75-0.96)	0.92 (0.76-1.12)	
College or higher	26,053	1.79 (0.81-3.94)	1.00	1.22 (0.83-1.81)	0.99 (0.55-1.79)	
Smoking						0.0024
Non-current smoker	333,263	1.68 (1.54-1.84)	1.00	0.92 (0.86-0.99)	1.00 (0.90-1.11)	

	Number	BMI (kg/m2)				$P_{interaction}$
Current smoker	118,996	1.87 (1.70-2.06)	1.00	0.82 (0.74-0.91)	0.82 (0.68-0.99)	
Physical activity[a]						0.0325
Low	150,351	1.76 (1.61-1.93)	1.00	0.88 (0.81-0.96)	0.93 (0.81-1.07)	
Middle	151,125	1.72 (1.53-1.93)	1.00	0.96 (0.87-1.06)	0.96 (0.81-1.14)	
High	150,783	1.82 (1.57-2.10)	1.00	0.81 (0.72-0.91)	0.97 (0.80-1.19)	
Menopause[b]						0.2271
No	122,093	1.38 (1.01-1.90)	1.00	0.81 (0.67-0.98)	0.88 (0.64-1.22)	
Yes	147,917	1.68 (1.52-1.86)	1.00	0.95 (0.87-1.04)	1.08 (0.96-1.23)	

Note: BMI, body mass index

Results were based on model 3. *P* values for interaction were calculated by likelihood ratio test comparing models with and without a cross-product term.

[a] Three groups were defined by gender-specific tertiles of metabolic Equivalent Task-hours.

[b] Among 270,010 female participants who had menopause status data at baseline

Table S3. Subgroup analysis for waist circumference and COPD according to age, area, education level, smoking status, physical activity, and menopause status

	Number	Waist circumference (cm)					$P_{interaction}$
		< 70 (male) < 65 (female)	70 to < 85 (male) 65 to < 80 (female)	85 to < 90 (male) 80 to < 85 (female)	90 to < 95 (male) 85 to < 90 (female)	≥ 95 (male) ≥ 90 (female)	
Age (years)							0.0094
<50	217,796	1.07 (0.88-1.30)	1.00	1.09 (0.93-1.28)	1.23 (1.01-1.50)	1.34 (1.04-1.72)	
50-59	139,336	1.20 (1.05-1.35)	1.00	1.18 (1.05-1.32)	1.27 (1.10-1.46)	1.70 (1.43-2.00)	
≥60	95,127	1.13 (1.04-1.24)	1.00	1.17 (1.07-1.27)	1.38 (1.25-1.54)	1.65 (1.46-1.87)	
Area							0.0019
Urban	197,228	1.47 (1.25-1.73)	1.00	1.09 (0.96-1.24)	1.16 (1.00-1.35)	1.30 (1.09-1.56)	
Rural	255,031	1.13 (1.05-1.22)	1.00	1.15 (1.07-1.24)	1.34 (1.22-1.46)	1.67 (1.50-1.86)	
Education							0.5551
Primary school or lower	224,483	1.19 (1.10-1.28)	1.00	1.16 (1.08-1.25)	1.30 (1.19-1.42)	1.57 (1.41-1.75)	
Middle/high School	201,723	1.01 (0.86-1.19)	1.00	1.14 (1.00-1.30)	1.32 (1.12-1.55)	1.64 (1.35-2.00)	
College or higher	26,053	1.53 (0.74-3.14)	1.00	1.19 (0.79-1.81)	1.54 (0.96-2.48)	1.37 (0.74-2.57)	
Smoking							0.8066

	Number	Waist circumference (cm)					$P_{interaction}$
Non-current smoker	333,263	1.25 (1.13-1.37)	1.00	1.14 (1.06-1.23)	1.25 (1.14-1.37)	1.43 (1.28-1.60)	
Current smoker	118,996	1.04 (0.94-1.14)	1.00	1.18 (1.06-1.32)	1.47 (1.27-1.69)	1.89 (1.59-2.25)	
Physical activity[a]							0.0002
Low	150,351	1.15 (1.04-1.27)	1.00	1.14 (1.04-1.25)	1.24 (1.11-1.39)	1.56 (1.36-1.78)	
Middle	151,125	1.16 (1.04-1.30)	1.00	1.07 (0.96-1.19)	1.35 (1.18-1.54)	1.43 (1.21-1.69)	
High	150,783	1.20 (1.05-1.38)	1.00	1.27 (1.11-1.45)	1.37 (1.16-1.62)	1.84 (1.51-2.25)	
Menopause[b]							0.9419
No	122,093	1.18 (0.89-1.57)	1.00	1.14 (0.93-1.40)	1.25 (0.95-1.64)	1.51 (1.08-2.11)	
Yes	147,917	1.30 (1.15-1.46)	1.00	1.15 (1.05-1.26)	1.28 (1.15-1.43)	1.39 (1.22-1.58)	

Note: Results were based on model 3. *P* values for interaction were calculated by likelihood ratio test comparing models with and without a cross-product term.

[a] Three groups were defined by gender-specific tertiles of metabolic Equivalent Task-hours.

[b] Among 270,010 female participants who had menopause status data at baseline

Table S4. Association of baseline waist-to-hip ratio and waist-to-height ratio with risk of COPD

	WHR			WHtR	
	<0.9 (male) <0.8 (female)	0.9-0.95 (male) 0.8-0.85 (female)	≥0.95 (male) ≥0.85 (female)	<0.5	≥0.5
Total (n=452,259)					
Cases	3,241	2,321	5,177	5,228	5,511
Rate (per/1000 person-years)	2.63	1.97	2.50	2.40	2.40
HR (95% CI) model 1	1.00	0.88 (0.83-0.93)	0.94 (0.90-0.99)	1.00	0.94 (0.90-0.98)
HR (95% CI) model 2	1.00	0.91 (0.86-0.96)	0.95 (0.91-1.00)	1.00	0.95 (0.91-0.99)
HR (95% CI) model 3	1.00	0.97 (0.91-1.02)	1.10 (1.04-1.17)	1.00	1.12 (1.07-1.19)
Male (n=182,209)					
Cases	2,631	1,299	1,283	3,151	2,062
Rate (per/1000 person-years)	3.29	2.50	2.80	3.32	2.49
HR (95% CI) model 1	1.00	0.89 (0.83-0.95)	0.97 (0.90-1.03)	1.00	0.87 (0.82-0.92)
HR (95% CI) model 2	1.00	0.91 (0.85-0.98)	0.98 (0.91-1.05)	1.00	0.90 (0.85-0.95)

HR (95% CI) model 3	1.00	1.09 (1.02-1.18)	1.37 (1.26-1.49)	1.00	1.29 (1.19-1.40)
Female (n=270,050)					
Cases	610	1,022	3,894	2,077	3,449
Rate (per/1000 person-years)	1.41	1.55	2.42	1.67	2.35
HR (95% CI) model 1	1.00	0.89 (0.81-0.99)	0.94 (0.86-1.03)	1.00	1.01 (0.96-1.07)
HR (95% CI) model 2	1.00	0.90 (0.81-1.00)	0.94 (0.86-1.03)	1.00	1.00 (0.95-1.06)
HR (95% CI) model 3	1.00	0.91 (0.82-1.01)	0.97 (0.88-1.06)	1.00	1.05 (0.98-1.13)

Note: WHR, waist-to-hip ratio; WHtR, waist-to-height ratio

Models were adjusted for: model 1: sex (only in total population); Model 2: additionally included education (none or primary school, middle or high school, college or university), marital status (married, widowed, divorced or separated, never married), smoking (never or occasional, former and having quitted <5, or ≥5 years, current smoking <15, 15 to 24, or ≥25 cigarettes/day), passive smoking (never lived with smoker, lived with smoker for <20 years, lived with smoker for ≥20 years and exposure < 20 hours/week, lived with smoker for ≥20 years and exposure ≥20 hours/week), cooking and heating fuel type (coal, wood/charcoal, cleaner fuel, other fuels, no cooking/heating), alcohol drinking (non-drinker, occasional drinker, former drinker, regular drinker), intake frequencies of red meat, fresh fruits, and vegetables (daily, 4-6 days/week, 1-3 days/week, monthly, rarely or never), physical activity (MET h/day), and respiratory symptoms (presence or absence); model3: additionally adjusted for BMI.

Table S5. Sensitivity analysis for the association between adiposity measures and COPD (HR and 95% CI)

	Among never smokers (n= 284,259)	Excluding cases in the first three years (n= 450,410)	LLN definition for airflow obstruction (n= 445,350)	Excluding prevalent diabetes (n= 424,045)
BMI (kg/m²)				
< 18.5	1.64 (1.48-1.81)	1.70 (1.58-1.83)	1.79 (1.67-1.90)	1.76 (1.64-1.88)
18.5 to < 24.0	1.00	1.00	1.00	1.00
24.0 to < 28.0	0.94 (0.87-1.02)	0.91 (0.86-0.97)	0.89 (0.84-0.95)	0.89 (0.84-0.94)
≥ 28.0	1.06 (0.94-1.20)	0.99 (0.90-1.10)	0.95 (0.86-1.04)	0.96 (0.87-1.06)
Waist circumference (cm)				
< 70 (male) < 65 (female)	1.26 (1.13-1.41)	1.19 (1.10-1.28)	1.17 (1.09-1.25)	1.16 (1.08-1.24)
70 to < 85 (male) 65 to < 80 (female)	1.00	1.00	1.00	1.00
85 to < 90 (male) 80 to < 85 (female)	1.15 (1.05-1.25)	1.10 (1.03-1.18)	1.15 (1.08-1.23)	1.15 (1.08-1.23)
90 to < 95 (male) 85 to < 90 (female)	1.25 (1.13-1.38)	1.20 (1.10-1.31)	1.31 (1.21-1.42)	1.31 (1.21-1.41)
≥ 95 (male) ≥ 90 (female)	1.40 (1.23-1.59)	1.48 (1.34-1.64)	1.57 (1.43-1.72)	1.58 (1.43-1.74)
WHR				
< 0.9 (male) < 0.8 (female)	1.00	1.00	1.00	1.00
0.9-0.95 (male) 0.8-0.85 (female)	0.90 (0.82-0.99)	0.96 (0.90-1.02)	0.97 (0.92-1.03)	0.96 (0.91-1.02)
≥ 0.95 (male) ≥ 0.85 (female)	0.97 (0.89-1.07)	1.06 (1.00-1.14)	1.11 (1.04-1.18)	1.11 (1.04-1.18)

	Among never smokers (n= 284,259)	Excluding cases in the first three years (n= 450,410)	LLN definition for airflow obstruction (n= 445,350)	Excluding prevalent diabetes (n= 424,045)
WHtR				
< 0.5	1.00	1.00	1.00	1.00
≥ 0.5	1.06 (0.98-1.15)	1.06 (1.00-1.13)	1.13 (1.07-1.19)	1.12 (1.06-1.18)

Note: BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; LLN, lower-limit of normal

Results were based on model 3