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Original article

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Overall and abdominal obesity and risks of all-cause and cause-specific mortality in Korean adults: a pooled analysis of three population-based prospective cohorts

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Abstract

Background: Studies found a J-shaped association between body mass index (BMI) and mortality. However, it is unclear whether the association is driven by biases, particularly confounding by fat-free mass.

Methods: We conducted an individual-level pooled analysis of three cohorts of Korean adults (aged $\geq$ 40 years; $n = 153\,248$). Mortality was followed up through December 2019. Anthropometric data were directly measured at baseline. Fat and fat-free mass were predicted using validated prediction models. Using Cox proportional hazards models, we estimated the associations of BMI and waist circumference (WC) with all-cause and cause-specific mortality. To account for biases, we excluded participants aged $\geq$ 70 years, deaths that occurred within 5 years of follow-up and ever smokers, and adjusted for fat-free mass index (FFMI).

Results: During the follow-up of up to 18 years, 6061 deaths were identified. We observed J-shaped association of BMI (nadir at 22–26) and monotonically positive association of WC with all-cause, cardiovascular, and cancer mortality among Korean adults without a history of cancer or cardiovascular disease. In the BMI analysis, excluding ever smokers and adjusting for FFMI attenuated the excess mortality in underweight participants and transformed the J-shaped association into a monotonically positive shape, suggesting an increased mortality at BMI $>$ 22.0. Excluding participants aged $\geq$ 70 years and deaths that occurred within 5 years of follow-up did not change the results. In the WC analysis, the monotonic positive associations did not change after the control. Similar results were observed among participants with a history of cancer or cardiovascular disease.

Conclusions: Our data suggest that both overall and abdominal body fat are associated with increased mortality in Korean adults.

Key words: Obesity, overweight, death, fat, adiposity, cardiovascular, cancer

Key Messages

- This study investigated the associations of body mass index (BMI) and waist circumference (WC) with mortality, with extensive control for potential biases including confounding by fat-free mass, among 153 248 Korean adults in a pooled analysis of three prospective cohorts.
- Controlling for confounding by smoking and fat-free mass transformed the J-shaped association between BMI and mortality into a monotonically positive shape, whereas the same control did not transform the monotonically positive association between WC and mortality.
- Our data suggest that both overall and abdominal body fat accumulation may be associated with increased risk of mortality in Korean adults, with no survival benefit of being overweight and obese compared with normal weight.

Introduction

Obesity is associated with increased risks of type 2 diabetes,[1,2] cardiovascular disease[3,4] and cancer,[5,6] which are major causes of deaths worldwide. To date, many studies have investigated the association between obesity and mortality, using body mass index (BMI) as a surrogate measure of overall body fat. These studies consistently reported a J-shaped association, showing increased mortality at both low and high BMI compared with intermediate BMI.[7–24] However, the magnitude of association and the specific range of BMI associated with lowest mortality varied across the studies.[7–24] The possible explanations for the discrepant findings include failure to account for confounding by smoking, reverse causation by pre-existing diseases, and differences in body composition (e.g. fat-free mass) and other population characteristics (e.g. age, race/ethnicity). Although some studies partially accounted for these methodological issues,[15,16,20,21,23,25–27] such as confounding by smoking and reverse causation by pre-existing diseases, only a few studies accounted for differences in body composition.[12,16,28] Because BMI cannot differentiate fat mass from fat-free mass, the BMI and mortality association is likely to reflect mixed effects of fat and fat-free mass and to vary across populations with different body composition (e.g. elderly vs. young,[29] Asian vs. Western populations[30]). In addition, BMI does not provide information on body fat distribution (overall vs. abdominal fat). For this reason, some studies used waist circumference (WC) as another surrogate measure of body fat, specifically abdominal fat, and reported positive associations with cardiometabolic diseases[31–33] and mortality.[34–38] However, it is as yet unknown whether the associations are independent of fat-free mass.

In this study, we examined the associations of BMI and WC with all-cause and cause-specific (cardiovascular and cancer) mortality, while carefully accounting for differences in age distribution, reverse causation by pre-existing diseases, confounding by smoking and confounding by fat-free mass, among 153 248 Korean men and women in a pooled analysis of three cohorts. We conducted a pooled analysis to include a large sample and a wide range of BMI and WC. Further, whereas previous studies have primarily focused on Western populations, this study examined the associations in Asians to provide additional insight into the relationship between obesity and mortality. We also accounted for body composition in the analysis by developing and validating prediction models that allowed the estimation of fat and fat-free mass in all study participants.

Methods

Study population

We conducted an individual-level pooled analysis of three population-based prospective cohort studies from South Korea: the Ansan and Ansung study (Ansan-Ansung),[39] the Health Examinee (HEXA) study[39] and the Cardiovascular Disease Association Study (CAVAS).[39] The Ansan-Ansung, HEXA and CAVAS are ongoing cohorts that are parts of the Korean Genome and Epidemiology Study, a large consortium project executed by the Korea Disease Control and

Prevention Agency (KDCA). The Ansan-Ansung began in 2001–02 and biannually followed up among 10 030 adults aged 40–69 years living in the city of Ansan (industrialized city; $n = 5012$) and Ansung (rural city; $n = 5018$). The HEXA began in 2004–13 among 173 343 adults aged ≥40 years who had health examinations at medical centres in 13 urban cities (Seoul, Busan, Incheon, Daegu, Gwangju, Ulsan, Anyang, Goyang, Seongnam, Chuncheon, Cheonan, Hwasun, Changwon). The CAVAS began in 2005–11 among 28 338 adults aged ≥40 years living in six rural areas (Yangpyeong, Goryeong, Namwon, Wonju, Pyeongchang, Ganghwa). In all three cohorts, the on-site health interview and physical examination were conducted at baseline to collect information on demographic characteristics, lifestyle, medical history and anthropometric and biochemical measurements. The questionnaires and survey methods were similar in all three cohorts. Among participants who agreed to mortality follow-up at the time of recruitment (78.7% in Ansan-Ansung, 75.2% in HEXA, 66.8% in CAVAS), the survey data were linked to their vital records through December 2019. Demographic characteristics were similar between those who agreed and did not agree to the mortality follow-up (Supplementary Table S1, available as Supplementary data at *IJE* online). All participants provided informed consent and all procedures were approved by the Ethics Committee of the KDCA and Korea University.

Among 157 042 pooled participants with mortality follow-up data ($n = 7894$ Ansan-Ansung; 130 227 HEXA; 18 921 CAVAS), we excluded participants who were currently pregnant ($n = 3025$), had BMI <13 or >50 kg/m^2 ($n = 153$), had WC <50 or >190 cm ($n = 428$) or died within 1 year of follow-up ($n = 188$) (participant flowchart in Supplementary Figure S1, available as Supplementary data at *IJE* online). After the exclusions, a total of 153 248 participants ($n = 7845$ Ansan-Ansung; 126 572 HEXA; 18 831 CAVAS) were included in our analysis.

Anthropometric measurement

During the physical examination, height, weight and WC were directly measured by trained medical staff following the standardized protocols. Height was measured to the nearest 0.1 cm using a stadiometer. Weight was measured to the nearest 0.1 kg on a scale, wearing a lightweight clothing with shoes off. WC was measured to the nearest 0.1 cm at the midpoint between the lower margin of the rib cage and the top of the iliac crest with minimal respiration. BMI (kg/m^2) was calculated as weight (kg) divided by height squared (m^2) and then categorized into five groups following the World Health Organization Asia-Pacific regional guidelines (<18.5, 18.5–22.9, 23.0–24.9, 25.0–29.9, ≥30.0 kg/m^2 for underweight, normal weight, overweight, grade I obesity, and grade II obesity, respectively).[40]

Because fat and fat-free mass were not measured in the study, we predicted these measures for all study participants using prediction models that we developed and validated against dual-energy X-ray absorptiometry (DXA) measurements, the gold standard for body composition measurement.[41,42] Detailed methods and the sex-specific prediction equations are presented in the Supplementary Methods (available as Supplementary data at *IJE* online). Briefly, among a nationally representative sample of 17 182 healthy Korean adults (7349 men and 9833 women) from the Korea National Health and Nutrition Examination Study (KNHANES) 2008–11 DXA examination, we developed and validated sex-specific prediction models for DXA-measured fat and fat-free mass (specifically, fat-free mass minus bone mass) using the information on age, height, weight, WC and current smoking status. The adjusted R^2 of the fat and fat-free mass prediction models were 0.74 and 0.85, respectively, in men (Supplementary Table S2, available as Supplementary data at *IJE* online) and 0.83 and 0.77, respectively, in women (Supplementary Table S3, available as Supplementary data at *IJE* online). Using the predicted values, we estimated fat mass index (FMI; kg/m^2) as predicted fat mass divided by height squared, and fat-free mass index (FFMI; kg/m^2) as predicted fat-free mass divided by height squared. Based on the sex-specific cut-points selected from the healthy reference adults in the KNHANES 2008–11 DXA examination, participants were classified into four body composition types: 'high fat-free/low fat mass' (FFMI >lowest tertile and FMI <highest tertile); 'low fat-free/low fat mass' (FFMI <lowest tertile and FMI <highest tertile); 'high fat-free/high fat mass' (FFMI >lowest tertile and FMI >highest tertile); and 'low fat-free/high fat mass' (FFMI <lowest tertile and FMI >highest tertile).

Mortality assessment

The current analysis was restricted to participants who agreed to mortality follow-up at the time of recruitment. In the pooled population, a total of 6061 deaths (621 Ansan-Ansung, 3559 HEXA, 1881 CAVAS) were identified via reviewing national death certificate records from Statistics Korea. The underlying causes of death were identified using codes from the 10th version of International Classification of Diseases. All-cause deaths, as well as cardiovascular (I00-I99) (1121 deaths; 134 Ansan-Ansung, 572 HEXA, 415 CAVAS) and cancer deaths (C00-D48) (2635 deaths; 226 Ansan-Ansung, 1767 HEXA, 642 CAVAS), were identified.

Prevalent conditions

In each cohort, a history of disease diagnosis (cancer, cardiovascular disease, hypertension, dyslipidaemia and type 2 diabetes) was self-reported via the baseline health interview. Blood cholesterol, triglyceride, glycated haemoglobin (HbA1c), fasting blood glucose, and blood pressure were directly measured during the baseline physical examination. Prevalent type 2 diabetes was defined as having a prior diagnosis of type 2 diabetes, having fasting blood glucose concentrations ≥126 mg/dL or HbA1c ≥6.5%, or currently taking diabetic medication. Prevalent hypertension was defined as having a prior diagnosis of hypertension, having measured systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or taking antihypertensive pills. Prevalent dyslipidaemia was defined as having a prior diagnosis of dyslipidaemia, having measured total cholesterol concentrations ≥240 mg/dL, high-density lipoprotein cholesterol concentrations ≤40 md/dL, low-density lipoprotein cholesterol concentrations ≥160 mg/dL or triglyceride concentrations ≥200 mg/dL, or taking medication or on treatment for dyslipidaemia.

Statistical analyses

Within each cohort, the follow-up of this analysis started when weight and height were measured during the baseline physical examination. Participants were followed from the baseline to the date of death or the end of follow-up on 31 December 2019, whichever occurred first. Using age as the underlying time metameter, Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of BMI and WC with all-cause and cause-specific mortality, stratified by cohort, survey years and survey districts. All multivariable models included potential confounders (sex, marital status, education attainment, household income, occupation, smoking status and alcohol intake which were self-reported at baseline) and a 1-y lag time. For WC analyses, we additionally adjusted for BMI in the models to estimate the independent association. Further, because most guidelines suggest different WC cut-points for men and women,[43–45] all WC analyses were conducted separately in each sex. For BMI, we stratified by sex in sensitivity analysis only.

Next, we extensively accounted for potential biases. First, we accounted for age distribution and related issues (e.g. presence of multiple pre-existing diseases and loss of fat-free mass in the elderly) by excluding participants aged ≥70 years. Second, we accounted for reverse causation due to pre-existing diseases by conducting all analyses separately in participants with and without a history of cancer or cardiovascular disease. Cancer and cardiovascular disease were considered because they are leading causes of death in Korea and may have contributed to weight change prior to the baseline. We further reduced reverse causation by excluding deaths that occurred during the first 5 years of follow-up. We also excluded participants with <10 years of follow-up in sensitivity analysis. Third, to extensively reduce confounding by smoking, we restricted the population to never smokers. Finally, we accounted for fat-free mass by additionally adjusting for FFMI in the multivariable models. In secondary analysis, we decomposed BMI into FMI and FFMI and separately examined the associations of the two components with mortality while adjusting for each other. In sensitivity analysis, we estimated the study-specific associations to assess whether the associations are consistent across the three cohorts. In all analyses, we examined the nonlinear shape of associations by performing restricted cubic spline models with five knots at the 5th, 35th, 50th, 65th and 95th percentiles.[46] We tested for potential nonlinearity using the likelihood ratio test that compares nonlinear restricted cubic spline models with linear models. When the relationships appeared linear (P-nonlinearity >0.05), tests for linear trend were performed using the Wald test for continuous variables.

To further understand the associations for BMI and WC, we estimated the proportion of each body composition type and the age- and sex-adjusted prevalences of type 2 diabetes, hypertension and dyslipidaemia according to BMI and WC categories. Because type 2 diabetes, hypertension and dyslipidaemia may be potential mediators, we did not adjust for these variables in the multivariable models for mortality. We performed the F test for analysis of variance (ANOVA) to assess any difference in distributions by exposure categories. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc.).

Results

Participant characteristics

During the follow-up, 153 248 participants (56 337 men, 96 911 women) contributed a total of 1 477 889 person-years (mean follow-up: 16.4 years in Ansan-Ansung, 9.1 years in HEXA, 10.7 years in CAVAS). BMI ranged 13.1–44.2: mean [standard deviation (SD): 24.0 (2.9)] and WC ranged 50.0–145.0: mean [SD: 81.5 (8.7)]. Compared with normal weight participants (BMI 18.5–22.9), those with higher BMI were more likely to have higher WC, lower than high school education, low

Table 1 Baseline characteristics of study participants according to body mass index (BMI) categories in the pooled population

	BMI (kg/m^2)				
	<18.5	18.5–22.9	23.0–24.9	25.0–29.9	≥30.0
Number of participants at the baseline	2,664	55,798	42,371	47,600	4,815
Age in years, mean (SD)	53.5 (10.3)	52.8 (8.8)	54.2 (8.5)	54.7 (8.5)	53.7 (8.6)
BMI in kg/m^2, mean (SD)	17.7 (0.7)	21.4 (1.1)	24.0 (0.6)	26.7 (1.3)	31.8 (1.9)
WC in cm, mean (SD)					
Men	70.3 (5.1)	79.2 (5.3)	85.0 (4.6)	90.7 (5.2)	100.8 (6.0)
Women	65.7 (5.0)	73.4 (5.6)	79.6 (5.3)	85.8 (6.0)	96.2 (6.9)
Sex, %					
Male	30.7	29.6	39.2	43.9	31.7
Female	69.3	70.4	60.8	56.1	68.3
Marital status, %					
Never married	1.7	1.2	0.9	1.0	1.7
Married	86.5	87.3	88.0	87.1	84.5
Divorced/separated	10.2	9.1	8.8	9.5	10.9
Missing	1.6	2.4	2.3	2.4	2.9
Education attainment, %					
Lower than high school	31.2	31.8	38.0	42.8	48.6
High school	39.3	42.1	38.5	35.0	32.8
College or higher	28.8	25.1	22.5	21.2	17.3
Missing	0.7	1.0	1.0	1.0	1.3
Household income, %					
Lowest	13.5	10.9	11.8	13.7	16.5
Mid to low	17.9	17.2	18.3	18.4	19.5
Mid to high	33.1	36.1	35.9	33.8	30.9
Highest	21.0	22.4	20.1	18.9	16.4
Missing	14.5	13.4	13.9	15.2	16.7
Occupation, %					
Non-physical labour	11.7	12.7	13.3	13.7	11.1
Physical labour	35.8	35.0	36.8	39.1	38.7
Unemployed/homemakers/soldiers/others	38.8	38.9	36.5	34.3	39.2
Missing	13.7	13.4	13.4	12.9	11.0
Smoking status, %					
Never smokers	74.5	76.3	70.2	66.5	73.6
Former smokers	9.8	11.5	16.7	19.3	14.4
Current smokers	15.7	12.2	13.1	14.2	12.0
Alcohol intake, %					
Never drinkers	58.7	52.7	48.5	47.2	52.6
Former drinkers	4.9	3.7	4.2	4.7	5.1
Current drinkers	36.1	43.1	46.8	47.7	41.8
Missing	0.3	0.5	0.5	0.4	0.5
History of cancer, %	5.4	3.4	3.0	2.7	2.8
History of cardiovascular disease, %	2.5	2.9	4.1	5.1	6.3

BMI, body mass index; SD, standard deviation; WC, waist circumference.

household income and a history of cardiovascular disease (Table 1).

Most participants with BMI ≥ 25.0 had 'high fat-free/high fat mass' body type and most participants with BMI < 23.0 had 'low fat-free/low fat mass' type (Figure 1A). The proportion of 'high fat-free/low fat mass' was highest in those with BMI 23.0–24.9. With increasing WC, the proportions of 'high fat-free/high fat mass' and 'low fat-free/high fat mass' types increased and the proportion of 'low fat-free/low fat mass' type decreased in both men (Figure 1B) and women (Figure 1C). The proportion of 'high fat-free/low fat mass' was highest in those with WC 80.0–84.9 in men and 75.0–79.9 in women. The prevalence of hypertension, dyslipidaemia and type 2 diabetes were higher in those with higher BMI (P <0.001; Figure 1D) and higher WC (P <0.001; Figure 1E and F).

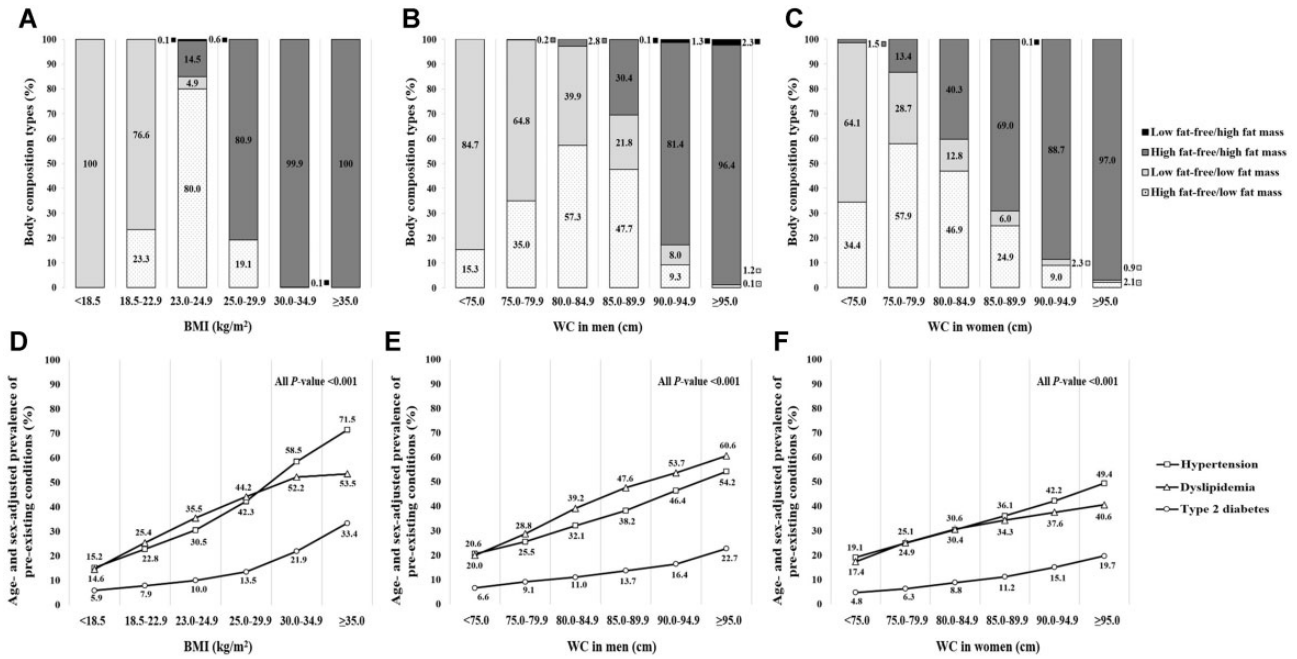

Figure 1 Baseline distribution of body composition types and pre-existing conditions according to BMI and WC in the pooled population. This figure shows the distribution of body composition types according to (A) BMI, (B) WC in men and (C), WC in women, and the distribution of pre-existing conditions according to (D) BMI, (E) WC in men and (F) WC in women, in the pooled population. In (A), (B) and (C), the body composition types were estimated based on predicted values of body fat and fat-free mass (fat-free mass minus bone mass). Using sex-specific cut-offs from a nationally representative sample of KNHANES Korean adult participants without a history of cardiovascular disease or cancer, we classified participants into four body composition types: 'high fat-free/low fat mass' (FFMI >lowest tertile and FMI <highest tertile); 'low fat-free/low fat mass' (FFMI <lowest tertile and FMI <highest tertile); 'high fat-free/high fat mass' (FFMI >lowest tertile and FMI >highest tertile); and 'low fat-free/high fat mass' (FFMI <lowest tertile and FMI>highest tertile). In (D), (E) and (F), hypertension was defined in individuals who had a previous diagnosis of hypertension, high measured blood pressure (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) at baseline or taking antihypertensive medicine. Dyslipidaemia was defined in individuals who had a previous diagnosis of dyslipidaemia, high measured total cholesterol ≥240 mg/dL, high triglyceride ≥200 mg/dL, high LDL cholesterol ≥160 mg/dL or low HDL cholesterol ≥40 mg/dL. Type 2 diabetes was defined in individuals who had a previous diagnosis of type 2 diabetes, high measured blood glucose ≥126 mg/dL or high HbA1c ≥6.5%. The prevalences of pre-existing conditions (hypertension, dyslipidaemia, type 2 diabetes) were adjusted for age and sex. *P*-value was estimated by F test for analysis of variance (ANOVA). BMI, body mass index; FFMI, fat-free mass index; FMI, fat mass index; KNHANES, Korea National Health and Nutrition Examination Survey; WC, waist circumference; LDL, low-desnsity lipoprotein; HDL, high-density lipoprotein

The overall distributions were similar between men and women (Supplementary Figure S2, available as Supplementary data at *IJE* online) and between participants with and without a history of cancer or cardiovascular disease (Supplementary Figure S3, available as Supplementary data at *IJE* online).

Mortality associations

Among participants without a history of cancer or cardiovascular disease, the associations of baseline BMI with all-cause, cardiovascular and cancer mortality were J-shaped, with the nadir ranging from BMI 22 to 26 (*P*-nonlinearity <0.001; Figure 2). Compared with normal-weight participants (BMI 18.5–22.9), the risk of all-cause mortality was statistically significantly higher in the underweight: BMI <18.5: HR (95% CI) = 1.64 (1.42, 1.90) and grade II obesity: BMI ≥30.0: 1.32 (1.13, 1.54) but was lower in the overweight: BMI 23.0–24.9: 0.89 (0.83, 0.96) and in grade I obesity: BMI 25.0–29.9: 0.91 (0.85, 0.98) (Table 2).

After adjustment for BMI, the associations of baseline WC with all-cause and cardiovascular mortality were monotonically positive (*P*-linearity ≤0.04; Figure 2). Compared with WC <75.0, higher WC was associated with higher all-cause and cardiovascular mortality in both men: WC ≥95.0: 1.40 (1.14, 1.72) all-cause; 2.02 (1.22, 3.36) cardiovascular, and women: WC 90.0–94.9: 1.24 (1.01, 1.52) all-cause; 1.62 (1.01, 2.59) cardiovascular (Table 2). The associations were not statistically significant for cancer mortality (*P*-linearity ≥0.06).

Among participants with a history of cancer or cardiovascular disease, the overall associations were similar (Table 2; and Supplementary Figure S4, available as Supplementary data at *IJE* online). Results were also similar between men and women (Supplementary Table S4, available as Supplementary data at *IJE* online) and in all

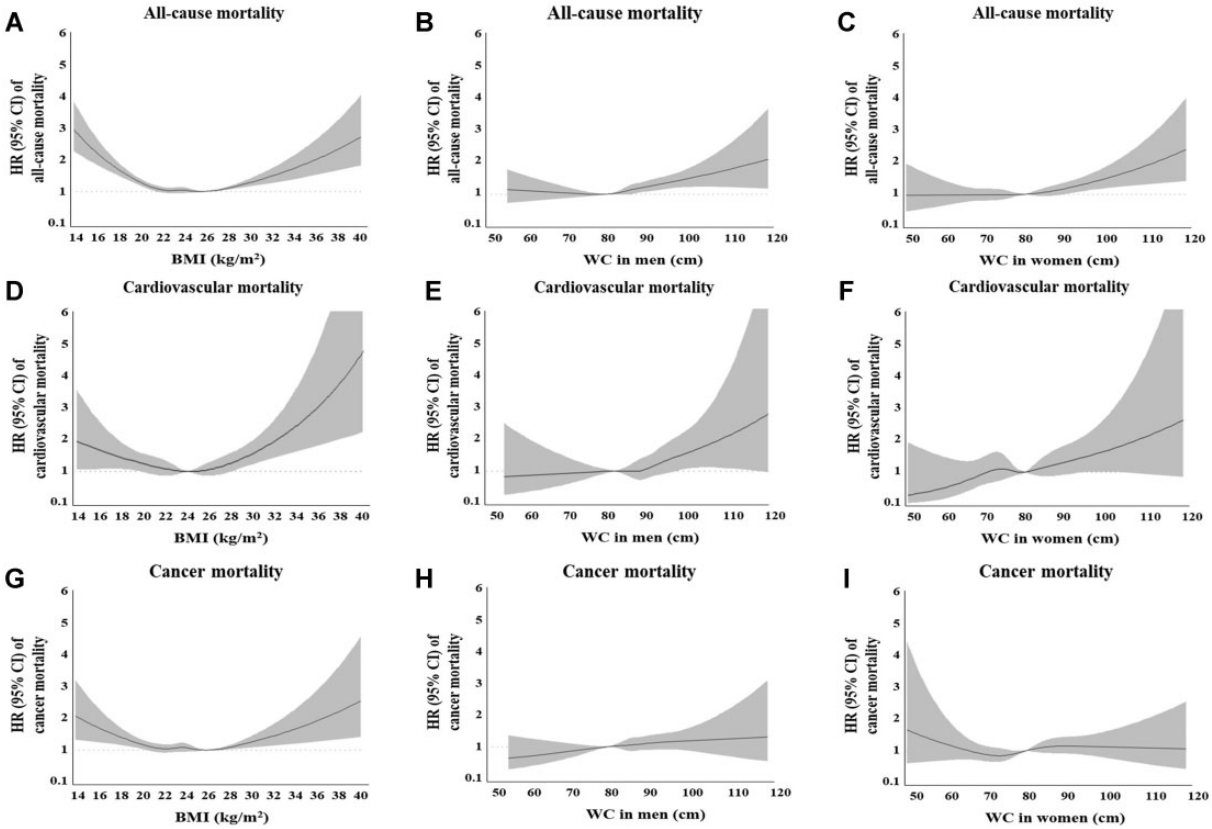

Figure 2 Dose-response relationships of BMI and WC with all-cause and cause-specific mortality among participants without a history of cancer or cardiovascular disease in the pooled population. This figure shows the nonlinear spline curves for the associations between (A) BMI and all-cause mortality, (B) WC and all-cause mortality in men, (C) WC and all-cause mortality in women, (D) BMI and cardiovascular mortality, (E) WC and cardiovascular mortality in men, (F) WC and cardiovascular mortality in women, (G) BMI and cancer mortality, (H) WC and cancer mortality in men, and (I) WC and cancer mortality in women. Among 142 557 participants without a history of cancer or cardiovascular disease, 5081 total deaths, 877 cardiovascular deaths and 2230 cancer deaths were included in the analyses. HRs are presented as solid lines and 95% CIs as shaded areas. Restricted cubic spline models were performed with five knots placed at the 5th, 35th, 50th, 65th and 95th percentiles. The reference value of BMI is 26 kg/m^2 for all-cause and cancer mortality and 24 kg/m^2 for cardiovascular mortality. The reference value of WC is 80 cm. *P*-nonlinearity was estimated using the likelihood ratio test comparing the restricted cubic spline model vs. linear model. For *P*-nonlinearity >0.05, *P*-linearity was estimated using the Wald test for continuous trend variables. For each figure, *P*-values from nonlinearity test are as follows: (A) *P*-nonlinearity <0.001, (B) *P*-nonlinearity = 0.11, *P*-linearity <0.001, (C) *P*-nonlinearity = 0.28, *P*-linearity = 0.002, (D) *P*-nonlinearity <0.001, (E) *P*-nonlinearity = 0.46, *P*-linearity = 0.02; (F) *P*-nonlinearity = 0.69, *P*-linearity = 0.04, (G) *P*-nonlinearity <0.001, (H) *P*-nonlinearity = 0.95, *P*-linearity = 0.06, (I) *P*-nonlinearity = 0.23, *P*-linearity = 0.18. All models were adjusted for age (years), marital status (never married/married/divorced or separated), education attainment (lower than high school/high school/college or higher), household income level (lowest/mid to low/mid to high/highest), occupation (non-physical labour/physical labour/unemployed, homemakers, soldiers, or others), smoking status (never smokers/former smokers/current smokers) and alcohol intake (never drinkers/former drinkers/current drinkers). Sex (male/female) was additionally adjusted for in BMI analyses, and BMI (<18.5/18.5–22.9/23.0–24.9/25.0–29.9/≥30.0) was additionally adjusted for in WC analyses. All analyses were stratified by cohort (Ansan-Ansung/HEXA/CAVAS), survey years (2001–13), and survey districts (Ansan, Ansung, 39 survey sites in urban areas and 11 rural counties). Ansan-Ansung, the Ansan and Ansung study; BMI, body mass index; CAVAS, the Cardiovascular Disease Association Study; CI, confidence interval; HEXA, the Health Examinee Study; HR, hazard ratio; WC, waist circumference

three cohorts (Supplementary Figure S5, available as Supplementary data at *IJE* online).

Mortality associations accounting for methodological issues

Figure 3 presents nonlinear spline curves for the BMI and mortality associations after accounting for four different methodological issues. After excluding participants aged ≥70 years and deaths that occurred within 5 years of follow-up, the J-shaped associations for BMI did not change (*P*-nonlinearity ≤0.01). When restricted to never smokers, the left tails of the curves were slightly flattened, showing a smaller magnitude of association with all-cause mortality and no association with cardiovascular and cancer mortality at BMI <22.0. Among never smokers, the nonlinearity of associations disappeared for cardiovascular (*P*-nonlinearity = 0.15) and cancer mortality (*P*-nonlinearity = 0.34)

Table 2 Associations of body mass index (BMI) and waist circumference (WC) with all-cause and cause-specific mortality in the pooled population, stratified by the history of cancer or cardiovascular disease ($n = 153\,248$)[a]

	Pooled population					
	All-cause mortality		Cardiovascular mortality		Cancer mortality	
	Case/PY	HR (95% CI)	Case/PY	HR (95% CI)	Case/PY	HR (95% CI)
Participants without a history of cancer or cardiovascular disease ($n = 142\,557$)						
BMI,[b] kg/m^2						
<18.5	209/22 588	**1.64 (1.42, 1.90)**	36/22 588	**1.49 (1.05, 2.11)**	60/22 588	1.27 (0.98, 1.66)
18.5–22.9	1832/498 781	1.00 (Ref)	302/498 781	1.00 (Ref)	779/498 781	1.00 (Ref)
23.0–24.9	1289/382 004	**0.89 (0.83, 0.96)**	211/382 004	0.94 (0.79, 1.13)	608/382 004	0.94 (0.85, 1.05)
25.0–29.9	1571/431 785	**0.91 (0.85, 0.98)**	298/431 785	1.14 (0.97, 1.34)	703/431 785	0.91 (0.83, 1.01)
≥30.0	180/43 650	**1.32 (1.13, 1.54)**	30/43 650	1.45 (0.99, 2.11)	80/43 650	**1.28 (1.02, 1.62)**
WC in men,[c] cm						
<75.0	350/38 196	1.00 (ref)	51/38 196	1.00 (ref)	123/38 196	1.00 (ref)
75.0–79.9	458/67 443	1.07 (0.92, 1.25)	83/67 443	1.41 (0.96, 2.06)	182/67 443	1.05 (0.82, 1.34)
80.0–84.9	659/123 515	1.05 (0.91, 1.23)	93/123 515	1.10 (0.74, 1.64)	312/123 515	1.12 (0.88, 1.42)
85.0–89.9	701/132 138	1.12 (0.95, 1.32)	105/132 138	1.21 (0.79, 1.84)	313/132 138	1.06 (0.82, 1.38)
90.0–94.9	539/90 495	**1.29 (1.07, 1.54)**	83/90 495	1.37 (0.86, 2.20)	243/90 495	1.20 (0.90, 1.59)
≥95.0	374/54 250	**1.40 (1.14, 1.72)**	79/54 250	**2.02 (1.22, 3.36)**	154/54 250	1.15 (0.84, 1.59)
WC in women,[c] cm						
<75.0	411/271 529	1.00 (ref)	61/271 529	1.00 (ref)	201/271 529	1.00 (ref)
75.0–79.9	387/202 185	0.96 (0.83, 1.11)	73/202 185	1.19 (0.83, 1.70)	173/202 185	0.91 (0.74, 1.13)
80.0–84.9	417/181 058	0.97 (0.82, 1.13)	78/181 058	1.14 (0.78, 1.69)	205/181 058	1.05 (0.83, 1.32)
85.0–89.9	349/118 536	1.01 (0.84, 1.21)	70/118 536	1.22 (0.80, 1.87)	165/118 536	1.12 (0.86, 1.46)
90.0–94.9	250/60 997	**1.24 (1.01, 1.52)**	56/60 997	**1.62 (1.01, 2.59)**	100/60 997	1.21 (0.89, 1.66)
≥95.0	186/38 466	1.24 (0.97, 1.58)	45/38 466	**1.85 (1.09, 3.15)**	59/38 466	0.99 (0.67, 1.46)
Participants with a history of cancer or cardiovascular disease ($n = 10\,691$)						
BMI,[b] kg/m^2						
<18.5	32/1814	1.37 (0.95, 1.98)	9/1814	1.64 (0.82, 3.29)	7/1814	0.73 (0.34, 1.57)
18.5–22.9	350/31 248	1.00 (ref)	82/31 248	1.00 (ref)	141/31 248	1.00 (ref)
23.0–24.9	257/27 265	**0.84 (0.72, 0.99)**	60/27 265	0.82 (0.59, 1.15)	116/27 265	0.94 (0.74, 1.21)
25.0–29.9	304/34 664	**0.78 (0.66, 0.91)**	86/34 664	0.92 (0.67, 1.25)	121/34 664	**0.75 (0.58, 0.95)**
≥30.0	37/4090	0.91 (0.64, 1.28)	7/4090	0.67 (0.31, 1.46)	20/4090	1.21 (0.75, 1.95)
WC in men,[c] cm						
<75.0	56/2564	1.00 (ref)	13/2564	1.00 (ref)	18/2564	1.00 (ref)
75.0–79.9	86/4390	1.24 (0.85, 1.80)	14/4390	0.97 (0.41, 2.31)	38/4390	1.34 (0.73, 2.46)
80.0–84.9	124/7890	1.15 (0.79, 1.69)	25/7890	1.11 (0.48, 2.56)	54/7890	1.15 (0.62, 2.12)
85.0–89.9	136/9870	1.13 (0.75, 1.69)	34/9870	1.34 (0.56, 3.23)	58/9870	1.03 (0.54, 1.98)
90.0–94.9	125/7919	1.30 (0.85, 2.01)	29/7919	1.45 (0.57, 3.70)	50/7919	1.06 (0.53, 2.13)
≥95.0	98/5406	1.60 (1.00, 2.56)	24/5406	1.65 (0.60, 4.57)	43/5406	1.43 (0.67, 3.04)
WC in women,[c] cm						
<75.0	70/14 749	1.00 (ref)	17/14 749	1.00 (ref)	33/14 749	1.00 (ref)
75.0–79.9	78/12 260	1.31 (0.93, 1.85)	25/12 260	1.74 (0.90, 3.36)	28/12 260	0.98 (0.57, 1.67)
80.0–84.9	61/13 899	0.85 (0.57, 1.26)	13/13 899	0.70 (0.32, 1.58)	28/13 899	0.97 (0.54, 1.74)
85.0–89.9	64/9657	1.15 (0.75, 1.76)	28/9657	1.75 (0.81, 3.77)	21/9657	1.07 (0.54, 2.12)
90.0–94.9	46/6237	1.23 (0.76, 2.02)	15/6237	1.45 (0.59, 3.59)	18/6237	1.53 (0.71, 3.33)
≥95.0	36/4240	1.21 (0.68, 2.16)	7/4240	1.06 (0.34, 3.34)	16/4240	1.63 (0.65, 4.09)

BMI, body mass index; PY, person-years; ref, reference; WC, waist circumference; Ansan-Ansung, the Ansan and Ansung study; CAVAS, the Cardiovascular Disease Association Study; HEXA, the Health Examinee Study.

[a]Bold text indicates nominal statistical significance at the α-level of 0.05.

[b]Adjusted for age (years), sex (male/female), marital status (never married/married/divorced or separated), education attainment (lower than high school/high school/college or higher), household income level (lowest/mid to low/mid to high/highest), occupation (non-physical labour/physical labour/unemployed, homemakers, soldiers, or others), smoking status (never smokers/former smokers/current smokers) and alcohol intake (never drinkers/former drinkers/current drinkers). Cox proportional hazards models were performed using age as the underlying time metameter. All analyses were stratified by cohort (Ansan-Ansung/HEXA/CAVAS), survey years (2001–13), and survey districts (Ansan, Ansung, 39 survey sites in urban areas and 11 rural counties).

[c]Adjusted for age (years), marital status (never married/married/divorced or separated), education attainment (lower than high school/high school/college or higher), household income level (lowest/mid to low/mid to high/highest), occupation (non-physical labour/physical labour/unemployed, homemakers, soldiers, or others), smoking status (never smokers/former smokers/current smokers), alcohol intake (never drinkers/former drinkers/current drinkers) and BMI (categorical, <18.5/18.5–22.9/23.0–24.9/25.0–29.9/≥30.0 kg/m^2). Cox proportional hazards models were performed using age as the underlying time metameter. All analyses were stratified by cohort (Ansan-Ansung/HEXA/CAVAS), survey years (2001–13) and survey districts (Ansan, Ansung, 39 survey sites in urban areas, and 11 rural counties).

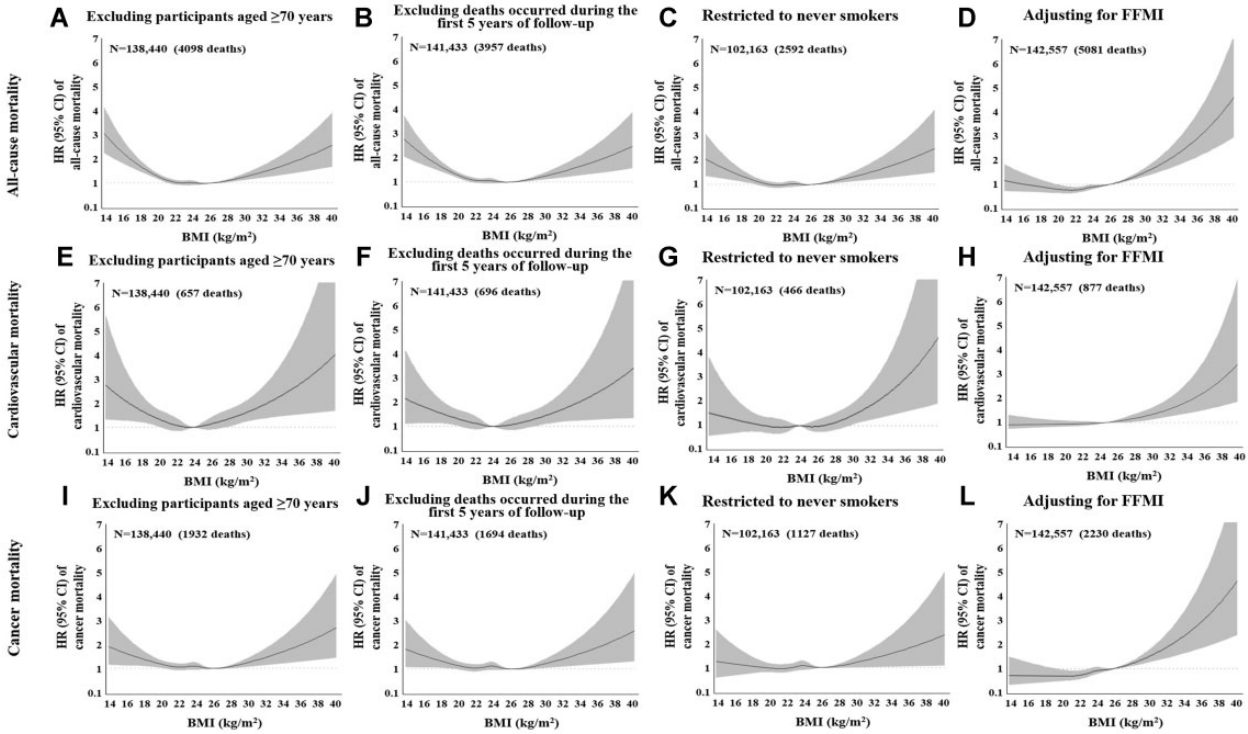

Figure 3 Dose-response relationships of BMI with all-cause and cause-specific mortality among participants without a history of cancer or cardiovascular disease in the pooled population, after controlling for four different methodological issues. This figure shows the nonlinear spline curves for: the association between BMI and all-cause mortality after (A) excluding participants aged ≥70 years, (B) excluding deaths that occurred during the first 5 years of follow-up, (C) restricting to never smokers and (D) adjusting for FFMI; the association between BMI and cardiovascular mortality after (E) excluding participants aged ≥70 years, (F) excluding deaths that occurred during the first 5 years of follow-up, (G) restricting to never smokers and (H) adjusting for FFMI; the association between BMI and cancer mortality after (I) excluding participants aged ≥70 years, (J) excluding deaths that occurred during the first 5 years of follow-up, (K) restricting to never smokers and (L) adjusting for FFMI. Among 142 557 participants (5081 deaths) without a history of cancer or cardiovascular disease at baseline, we accounted for age distribution and related issues by excluding 4117 participants aged ≥70 years. We reduced reverse causation due to subclinical diseases by excluding 1124 deaths that occurred during the first 5 years of follow-up. To reduce confounding by smoking, we restricted the population to never smokers by excluding 40 394 ever smokers. FFMI (continuous, decile) was adjusted as a covariate in the models. HRs are presented as solid lines and 95% CIs as shaded areas. Restricted cubic spline models were performed with five knots placed at the 5th, 35th, 50th, 65th, and 95th percentiles. The reference value of BMI is 26 kg/m^2 for all-cause and cancer mortality and 24 kg/m^2 for cardiovascular mortality. FFMI was calculated as predicted fat-free mass (kg) divided by height squared (m^2). Predicted fat-free mass was estimated from validated prediction models developed based on the KNHANES DXA data 2008–11. *P*-nonlinearity was estimated using the likelihood ratio test comparing the restricted cubic spline model vs. linear model. For *P*-nonlinearity >0.05, *P*-linearity was estimated using the Wald test for continuous trend variables. For each figure, *P*-nonlinearity and/or *P*-linearity are as follows: (A) *P*-nonlinearity <0.001, (B) *P*-nonlinearity <0.001, (C) *P*-nonlinearity <0.001, (D) *P*-nonlinearity <0.001, (E) *P*-nonlinearity <0.001, (F) *P*-nonlinearity = 0.01, (G) *P*-nonlinearity = 0.15, *P*-linearity = 0.02, (H) *P*-nonlinearity = 0.05, *P*-linearity <0.001, (I) *P*-nonlinearity = 0.003, (J) *P*-nonlinearity = 0.01, (K) *P*-nonlinearity = 0.34, *P*-linearity = 0.10, (L) *P*-nonlinearity = 0.08, *P*-linearity <0.001. All models were adjusted for age (continuous, years), sex (male/female), marital status (never married/married/divorced or separated), education attainment (lower than high school/high school/college or higher), household income level (lowest/mid to low/mid to high/highest), occupation (non-physical labour/physical labour/unemployed, homemakers, soldiers, others), smoking status (never smokers/former smokers/current smokers) and alcohol intake (never drinkers/former drinkers/current drinkers). All analyses were stratified by cohort (Ansan-Ansung/HEXA/CAVAS), survey years (2001–13) and survey districts (Ansan, Ansung, 39 survey sites in urban areas and 11 rural counties). Ansan-Ansung, the Ansan and Ansung study; BMI, body mass index; CAVAS, the Cardiovascular Disease Association Study; CI, confidence interval; DXA, dual-energy X-ray absorptiometry; FFMI, fat-free mass index; HEXA, the Health Examinee Study; HR, hazard ratio; KNHANES, Korea National Health and Nutrition Examination Survey

and the linear trend with cardiovascular mortality became statistically significant (*P*-linearity = 0.02). After adjustment for FFMI, the associations markedly changed into a monotonically positive shape, showing no increased mortality at BMI <22.0 and a gradual increase in mortality at BMI >22.0. The linear trends for cardiovascular (*P*-linearity <0.001) and cancer mortality (*P*-linearity <0.001) became statistically significant after adjustment for FFMI.

No further change was observed after excluding participants with <10 years of follow-up (Supplementary Figure S6, available as Supplementary data at *IJE* online) or after simultaneous exclusions of participants aged ≥70 years, deaths that occurred within 5 years of follow-up and ever smokers (Supplementary Figure S7, available as Supplementary data at *IJE* online). For WC, excluding participants aged ≥70 years and deaths that occurred within

5 years of follow-up, restricting to never smokers and adjusting for FFMI did not considerably change the associations with all-cause, cardiovascular and cancer mortality (Supplementary Figure S8 and S9, available as Supplementary data at *IJE* online). When we separately examined the associations of FMI and FFMI while adjusting for each other, we confirmed monotonically positive associations of FMI and monotonically inverse associations of FFMI with all-cause, cardiovascular and cancer mortality (Supplementary Figure S10, available as Supplementary data at *IJE* online).

Discussion

In our pooled analysis of three cohorts, we observed a J-shaped association between BMI and mortality and a monotonically positive association between WC and mortality among Korean men and women without a history of cancer or cardiovascular disease. In the BMI analysis, excluding ever smokers and adjusting for FFMI attenuated the excess mortality risk in underweight (vs. normal-weight) participants and transformed the overall J-shaped associations into a monotonically positive shape, suggesting increasing mortality at BMI >22.0. In the WC analysis, the monotonic positive associations did not change after accounting for these methodological issues. Among participants with a history of cancer or cardiovascular disease, the overall results were similar. Our data suggest that both BMI (with extensive control for biases) and WC (even without such control), the two surrogate measures of body fat, are monotonically positively associated with mortality in Korean adults.

In this study, the positive association between underweight BMI and mortality was slightly attenuated after excluding ever smokers, suggesting that the association may be at least partially explained by confounding due to smoking. Smokers have higher mortality[47] and are more likely to have lower BMI due to pre-existing diseases and exposure to nicotine that activates mechanisms leading to weight loss.[48] Because duration and cumulative amount of smoking may widely vary among smokers, the adjustment for smoking status as a covariate in the models may not be adequate in controlling for confounding. Further, smokers with low BMI are likely to have lower fat-free mass because smoking may accelerate muscle protein breakdown and amplify inflammatory response that precludes protein synthesis.[49–53] For this reason, excluding smokers may also partially reduce confounding by fat-free mass.

The largest change in the BMI and mortality association was observed when we adjusted for FFMI. After the adjustment, the association became monotonically positive, showing increasing mortality with increasing BMI. Our finding suggests that, after accounting for possible adverse effects from low fat-free mass, the true biological effect of body fat is likely to be detrimental. Studies have shown that accumulation of body fat is associated with inflammation,[54] insulin resistance,[55] glucose intolerance[56] and dyslipidaemia.[57] Low fat-free mass, specifically muscle mass, may also increase mortality by altering regulation of whole-body metabolism and inflammation.[58,59] Without the adjustment of FFMI, the mixed effects of fat and fat-free mass are likely to have created the J-shaped association between BMI and mortality. In our study, the nadir of the J-shape (BMI 22.0–26.0) also corresponded to the BMI range (23.0–24.9) with the highest proportion of 'high fat-free/low fat mass' body type, further supporting the role of body composition in the BMI-mortality association. Further, because the loss of fat-free mass is frequently observed in patients with certain diseases,[60,61] it is also possible that the adjustment of FFMI reduced reverse causation by subclinical disease that was not sufficiently captured by the exclusion of early deaths.

In contrast to excluding ever smokers and adjusting for FFMI, other methods of controlling biases had less impact on the BMI and mortality association. After excluding participants aged ≥70 years and deaths that occurred within 5 years of follow-up, we observed no substantial change in the association. Our finding suggests that the associations were less likely to have been driven by the excluded participants, as most participants were aged 40–69 years (97%) and followed up for >5 years (99%). It is also possible that, before these exclusions, we had already adequately controlled for biases due to age and pre-existing diseases, using age adjustment and stratification by disease history. Consistently, most studies that controlled for potential biases due to old age[7,8,10,11,13,26,27,62,63] and short follow-up[18–21,23,25–27,64] showed that the J-shaped association did not change after the control. Although a recent study suggested that at least 10–15 years of excluded follow-up may be needed to remove biases,[65] we observed no change in the association after excluding participants with <10 years of follow-up.

The association between WC and mortality did not substantially change after the extensive control for biases. The robustness of our result suggests that the monotonic positive association between WC and mortality is unlikely to be driven by reverse causation due to subclinical disease and confounding by smoking and fat-free mass. It is also possible that, with the adjustment of BMI, WC may better reflect fat mass, rather than fat-free mass. According to previous studies, WC closely reflects visceral and subcutaneous abdominal fat accumulation rather than lean mass or subcutaneous fat accumulation in arms and legs.[36,66,67] Visceral fat accumulation is associated with insulin

resistance,[55] chronic inflammation[68,69] and increased risks of cardiometabolic diseases[68–73] and various types of cancer.[74–77] Further, the monotonic positive association of WC is consistent with our finding of a substantial proportion of participants with 'high fat-free/low fat mass' type in low WC (<75.0). On the contrary, there was no participant with 'high fat-free/low fat mass' type in low BMI (<18.5).

In the current study, without extensive control for biases we initially observed a J-shaped association between BMI and mortality with the nadir at BMI 22.0–26.0, suggesting the lowest mortality at overweight BMI (23.0–24.9). The J-shaped association between BMI and mortality is consistent with previous studies from Korean[11,16] and other Asian populations,[20,23,24] although the range of nadir varied from 20.0 to 34.9. Similar to our finding, a pooled analysis of East Asian cohorts, including those from China, Japan and Korea, reported the lowest mortality at BMI 22.6–27.5.[23] Our previous study, using a nationally representative sample of Korean adults from the KNHANES, also reported a J-shaped association with the nadir at a slightly higher range of BMI (25.0–29.9).[16] These findings of lower mortality among the overweight and obese compared with the normal-weight population have been known as the 'obesity paradox'. The obesity paradox may be due to either the true biological effects of body fat or to methodological biases. Some studies suggested that higher BMI may be associated with improved survival in cancer patients.[78–80] However, based on our finding, it is likely that the obesity paradox has been largely driven by underweight participants with low fat-free mass[16,81] and smokers who are at increased risks of death-causing diseases.[82,83]

Our study has several important strengths. First, by including data from three independent cohorts, we increased sample size and thus had higher statistical power. These cohorts also included populations from different regions of Korea with a wider range of exposures. Second, we reduced measurement errors in exposures by using directly measured anthropometric data. Further, whereas many large studies lack information on body composition, we used fat and fat-free mass that were predicted from validated prediction models to account for body composition in a large analysis. Most prediction models were developed in Western populations, but we increased the validity of our prediction models by developing and validating them in a nationally representative sample of Korean adults.

This study also has several limitations. First, we used anthropometric data measured at baseline only and thus we were not able to account for changes in BMI and WC during the follow-up. Second, compared with directly measured data, our predicted measures of fat and fat-free mass may have greater measurement errors. However, in our validation analysis, our predicted measures were very close to the DXA measurements (mean difference ≤0.06 kg). This method has also been validly used in many studies.[12,16,84–88] Third, we used self-reported covariate data such as alcohol consumption and smoking status, which may be subject to misclassification. The misclassification in covariate data may result in inadequate control for confounding. Last, our study included Korean adults aged ≥40 years and thus our study results may not be generalizable to other racial populations or younger age groups.

Conclusions

In summary, BMI (with extensive control for biases) and WC (even without such control) were monotonically positively associated with all-cause, cardiovascular and cancer mortality among Korean adults. Our data suggest that, independently of fat-free mass, both overall and abdominal body fat may be associated with increased mortality. Our findings also highlight the importance of decomposing BMI into fat and fat-free mass when studying the association for obesity. Acknowledgement of the differential effects of fat and fat-free mass, both FMI and FFMI rather than BMI alone, may be recommended for use in clinic settings when identifying high-risk populations. When the direct measurement of body composition is not feasible, the validated prediction models can be useful in predicting this. To prevent premature death, preventive strategies need to focus on reducing body fat as well as increasing muscle mass. Future studies of obesity are recommended to carefully account for body composition, particularly for confounding by fat-free mass.

Ethics approval

This investigation was approved by the Institutional Review Board of Korea Disease Control and Prevention Agency and Korea University (IRB-2021–0054).

Data availability

Data described in the manuscript, code book and analytical code will be made available upon request and approval from KDCA (https://nih.go.kr/biobank/cmm/main/engMainPage.do).

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

H.J. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. H.O. conceptualized and designed the study, obtained the funding and supervised the research. H.J. performed statistical analysis and wrote the paper. R.K., J.T.L., D.H.L., E.L.G. and H.O. made substantial contributions to the interpretation of data and the critical revision and editing of the manuscript. All authors revised the manuscript for important intellectual content and read and approved the final manuscript.

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Conflict of interest

None declared.

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