Adiposity-Mortality Relationships in Type 2 Diabetes, Coronary Heart Disease, and Cancer Subgroups in the UK Biobank, and Their Modification by Smoking

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OBJECTIVE

The obesity paradox in which overweight/obesity is associated with mortality benefits is believed to be explained by confounding and reverse causality rather than by a genuine clinical benefit of excess body weight. We aimed to gain deeper insights into the paradox through analyzing mortality relationships with several adiposity measures; assessing subgroups with type 2 diabetes, with coronary heart disease (CHD), with cancer, and by smoking status; and adjusting for several confounders.

RESEARCH DESIGN AND METHODS

We studied the general UK Biobank population (*N* = 502,631) along with three subgroups of people with type 2 diabetes (*n* = 23,842), CHD (*n* = 24,268), and cancer (*n* = 45,790) at baseline. A range of adiposity exposures were considered, including BMI (continuous and categorical), waist circumference, body fat percentage, and waist-to-hip ratio, and the outcome was all-cause mortality. We used Cox regression models adjusted for age, smoking status, deprivation index, education, and disease history.

RESULTS

For BMI, the obesity paradox was observed among people with type 2 diabetes (adjusted hazard ratio for obese vs. normal BMI 0.78 [95% CI 0.65, 0.95]) but not among those with CHD (1.00 [0.86, 1.17]). The obesity paradox was pronounced in current smokers, absent in never smokers, and more pronounced in men than in women. For other adiposity measures, there was less evidence for an obesity paradox, yet smoking status consistently modified the adiposity-mortality relationship.

CONCLUSIONS

The obesity paradox was observed in people with type 2 diabetes and is heavily modified by smoking status. The results of subgroup analyses and statistical adjustments are consistent with reverse causality and confounding.

The obesity paradox refers to the commonly observed epidemiological finding that being overweight (BMI 25 to $<$30 kg/m^2) or obese (BMI $\geq$30 kg/m^2) is associated with longer survival than being normal weight (1–3). This finding has been observed in patients with coronary heart disease (CHD) (4), heart failure (5), cancer (6,7), and

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type 2 diabetes (8–10), among many other conditions. The idea that being overweight or obese has survival advantages is contrary to known pathophysiological mechanisms linking obesity to adverse outcomes. The extent to which the paradox represents statistical biases (11–13) versus genuine benefits of excess body weight is clinically important.

The obesity paradox has been extensively explored with regard to BMI but less often in relation to other measures of adiposity. BMI is an imprecise measure of body fat, and we took the opportunity to relate additional measures of adiposity to mortality by using UK Biobank data (14,15). The UK Biobank is an individual person health data resource with vast amounts of information, including variables that are potential confounders of relationships between adiposity measures and mortality.

We therefore assessed the relationships between several measures of adiposity and mortality in a prospective cohort of UK Biobank participants, including subgroups with type 2 diabetes, CHD, and cancer. We also quantified the interaction effect of smoking status in these relationships.

RESEARCH DESIGN AND METHODS

Study and Disease Subgroups

The UK Biobank recruited 502,631 participants aged 40–69 years between 2006 and 2010. All participants provided health, lifestyle, and sociodemographic data through questionnaires and interviews; underwent a physical examination; provided blood, urine, and saliva samples; and agreed to be followed for health outcomes. To facilitate follow-up, a wide range of databases, such as cancer and death registries, have been linked to UK Biobank.

We studied the whole UK Biobank cohort and three subgroups. These subgroups were participants with *1*) type 2 diabetes defined using a validated algorithm (16); *2*) CHD, defined as participants with angina, myocardial infarction, coronary angioplasty/stent, or coronary artery bypass surgery before recruitment; and *3*) cancer, as diagnosed in the cancer registry before the UK Biobank assessment center date.

Assessment and Classification of Adiposity, Confounders, and Outcomes

Baseline questionnaires collected information on smoking status, ethnicity, education, disease history, and other characteristics. Clinical examination by a nurse collected data on height, weight, body fat percentage, and waist and hip circumference (methods described at http://biobank.ctsu.ox.ac.uk/crystal). The deprivation index score was calculated by postal codes on the basis of national census data. Incident cancer and all-cause mortality information were obtained from national registries linked to UK Biobank.

BMI, calculated as weight in kilograms divided by height in meters squared, was analyzed both as a continuous variable, with a reference value of 22.5 kg/m^2, and as a categorical variable on the basis of World Health Organization (WHO) classifications. We split the WHO 18.5–25 kg/m^2 category into two groups, as in previous literature (9,17). The BMI categories used were $<$18.5, 18.5–22.4, 22.5–24.9 (reference), 25.0–29.9, 30.0–39.9, and $\geq$40.0 kg/m^2. Body fat percentage was estimated through bioelectrical impedance and treated as a continuous variable, with a reference obtained from WHO recommendations of 25% for men and 32% for women. Waist circumference and waist-to-hip ratio (WHR) reference values for women were 80 cm and 0.85, respectively, and for men, 94 cm and 0.9, respectively, on the basis of the WHO classification and recommendations (18). Smoking status was defined as a categorical variable: current, past, never, and unknown.

Deaths were identified from the death registry linked to the UK Biobank data. ICD-10 codes were used to identify the primary cause of death. Cancer deaths were defined as ICD-10 codes C00–C97 and cardiovascular deaths as I00–I99, E10.5, E11.5, E12.5, E13.5, or E14.5. Deaths with other ICD-10 codes as the primary cause were labeled as death as a result of other causes.

Statistical Analyses

The exposure was adiposity assessed as BMI, body fat, waist circumference, or WHR, and the outcome was mortality. Survival analysis was conducted in the whole UK Biobank cohort and in the diabetes, CHD, and cancer subgroups separately and then further stratified by smoking status (current, past, and never).

We used Cox proportional hazards regression models with age as the time scale, left truncated at study entry, and the outcome was age at death recorded in the death registry. All-cause mortality was the outcome for the primary analysis, and the three cause-specific mortalities were secondary outcomes. Individuals with no death recorded were censored at their attained age 1 month before the last death observed in the whole UK Biobank cohort to account for the potential lag time in recording deaths.

Separate models were constructed for individual adiposity measures, and these included cubic splines (19) for continuous predictor variables to provide the flexibility to identify any nonlinear (e.g., J-shaped) relationships. Nonlinearity was tested for by performing likelihood ratio tests, and the best-fitting model was chosen by assessing the Bayesian information criterion. We explored relationships between baseline adiposity measures and time to death by unadjusted models and models adjusted for age, sex, smoking status, ethnicity, education, deprivation index, and chronic diseases (renal failure, liver failure, heart failure, dementia, and cancer) diagnosed before study entry. Diabetes duration was not significantly related to mortality risk and was not included as a covariate. Proportionality was checked using Schoenfeld residuals, and models were stratified on variables that were found to violate proportionality. The BMI associated with the lowest mortality was obtained as the value with the smallest hazard ratio (HR), with bootstrapped CIs.

We considered the obesity paradox to be present in a cohort if a BMI value $>$25 kg/m^2 or adiposity measure above the reference value was associated with significantly longer survival than its reference. The modifying effect of smoking on the paradox also was tested by including a smoking interaction with adiposity.

Data analysis was performed using Stata 14 (StataCorp, College Station, TX) and R version 3.4.2 statistical software. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

The final cohort comprised 229,170 men and 273,461 women. A total of 212,166 participants (42%) were overweight, of whom 47% were women, whereas the underweight and most obese BMI categories were made up of predominantly women (79% and 63%, respectively) (Table 1). The highest percentage of smokers (23%) was observed among the underweight

Table 1—Baseline characteristics by BMI category

	BMI category (kg/m^2)					
Characteristic	<18.5	18.5–22.49	22.5–24.9	25–29.9	30–39.9	≥40
Participants	2,626 (0.52)	59,538 (11.85)	102,909 (20.47)	212,166 (42.21)	112,581 (22.40)	12,811 (2.55)
Female	2,079 (79.17)	43,980 (73.87)	61,709 (59.96)	99,904 (47.09)	57,682 (51.24)	8,107 (63.28)
Age (years)*	55.47 (8.16)	54.9 (8.27)	56.13 (8.17)	57.01 (8.06)	56.97 (7.89)	55.69 (7.85)
Ethnicity						
White European	2,438 (92.84)	56,372 (94.68)	97,516 (94.76)	200,043 (94.29)	105,354 (93.58)	11,091 (86.57)
South Asian	44 (1.68)	808 (1.36)	1,661 (1.61)	3,543 (1.67)	1,666 (1.48)	345 (2.69)
African Caribbean	10 (0.38)	453 (0.76)	1,042 (1.01)	3,257 (1.54)	2,777 (2.47)	526 (4.11)
Mixed or other	112 (4.27)	1,657 (2.78)	2,272 (2.21)	4,342 (2.05)	2,160 (1.92)	364 (2.84)
Deprivation index*	−0.67 (3.41)	−1.36 (3.07)	−1.57 (2.96)	−1.44 (3.02)	−0.9 (3.23)	0.09 (3.46)
Education						
College or university degree	1,059 (40.33)	25,105 (42.17)	38,668 (37.57)	65,967 (31.09)	27,561 (24.48)	2,845 (22.21)
Smoking status						
Never	1,474 (56.13)	35,883 (60.27)	59,747 (58.06)	113,066 (53.29)	56,883 (50.53)	6,543 (51.07)
Previous	540 (20.56)	15,923 (26.74)	31,893 (30.99)	76,322 (35.97)	43,994 (39.08)	4,422 (34.52)
Current	598 (22.77)	7,529 (12.65)	10,842 (10.54)	21,693 (10.22)	10,969 (9.74)	1,358 (10.60)
Chronic disease						
Hyperlipidemia	11 (0.42)	263 (0.44)	765 (0.74)	2,788 (1.31)	2,412 (2.14)	331 (2.58)
Renal failure	47 (1.79)	386 (0.64)	715 (0.69)	2,187 (1.03)	2,041 (1.81)	478 (3.73)
Liver failure	4 (0.15)	35 (0.06)	56 (0.05)	143 (0.07)	116 (0.10)	7 (0.05)
Heart failure	47 (1.79)	432 (0.73)	824 (0.80)	2,633 (1.24)	2,589 (2.30)	574 (4.48)
Dementia	8 (0.30)	125 (0.21)	212 (0.21)	473 (0.22)	292 (0.26)	51 (0.40)
Cancer	306 (11.70)	5,806 (9.75)	9,657 (9.38)	18,827 (8.87)	10,066 (8.94)	1,128 (8.80)
Diabetes	29 (1.10)	573 (0.96)	1,745 (1.70)	7,993 (3.77)	11,146 (9.90)	2,356 (18.39)
CHD	55 (2.09)	1,128 (1.89)	2,898 (2.82)	10,483 (4.94)	8,621 (7.66)	1,083 (8.45)

Data are *n* (%) unless otherwise indicated. *Data are mean (SD).

participants (BMI <18.5 kg/m^2) compared with 10% among obese participants. Data on BMI, body fat percentage, waist circumference, and WHR were available in 99%, 98%, 99%, and 99% of participants, respectively.

Of the 23,842 participants with type 2 diabetes, 13,502 (56.6%) were obese as were 9,704 of the 24,268 participants with CHD (40%). The remaining baseline characteristics had comparable proportions across BMI categories.

A total of 14,421 deaths were observed over a mean follow-up of 7.8 years. Of participants who died, 1,723 (11.9%) had type 2 diabetes, 2,004 (13.9%) had CHD, and 3,212 (22.2%) had cancer recorded at baseline. Cancer- and cardiovascular-related deaths amounted to 57.5% (*n* = 8,286) and 20.8% (*n* = 2,998) of all deaths, respectively.

Relationship Between BMI Categories and Mortality

In all groups, we observed U-shaped relationships between BMI categories and mortality (Fig. 1). Among all UK Biobank participants, being underweight was associated with a higher mortality risk than normal weight. This association was stronger among men (HR 3.28 [95% CI 2.62, 4.11]) than women (1.72 [1.37, 2.16]; *P* for interaction < 0.001) in the overall population.

Morbidly obese individuals (≥40 kg/m^2) had higher mortality than normal weight individuals in the overall population, but not in the type 2 diabetes or women with CHD subgroups. In the type 2 diabetes group, being obese was associated with lower mortality than being normal weight (HR 0.78 [95% CI 0.65, 0.95]), and this appeared to be driven by a lower hazard in men with type 2 diabetes (0.74 [0.60, 0.92]), whereas in women with type 2 diabetes did not have a statistically lower mortality risk (1.13 [0.73, 0.1.75]). Hence, in the categorical analyses, the obesity paradox was present only in men with type 2 diabetes. Compared with participants with normal weight, being overweight was associated with a lower mortality risk only in men with type 2 diabetes (0.74 [0.59, 0.92]).

Relationship Between Continuous BMI and All-Cause Mortality

Consistent with the categorical BMI data, we observed a U-shaped relationship between BMI and all-cause mortality among all groups (Fig. 2); low and high BMI values were associated with higher mortality than a BMI of 22.5 kg/m^2. Within the whole UK Biobank population, the lowest mortality was observed at a BMI of 27.2 kg/m^2 (mortality HR 0.83 [95% CI 0.80, 0.86]; reference BMI 22.5 kg/m^2) (Supplementary Table 1), whereas among participants with type 2 diabetes, the BMI with the lowest mortality risk was much higher (women 34.1 kg/m^2, men 31.7 kg/m^2). Among those with CHD, the lowest mortality rates were observed at a BMI of 29.4 kg/m^2 in women and 29.9 kg/m^2 in men.

Effect of Smoking on Relationships Between Continuous BMI and Mortality

In men, the obesity paradox was evident in smokers but not in nonsmokers (*P* for interaction = 0.002) (Fig. 3). The paradox was still present in men who had previously smoked but to a lesser extent than in current smokers. In particular, obese smokers had lower mortality than normal weight smokers. In contrast, obese nonsmokers had higher mortality than normal weight nonsmokers, and only those in the overweight range had lower mortality. In all women, however, no evidence of the obesity paradox was observed.

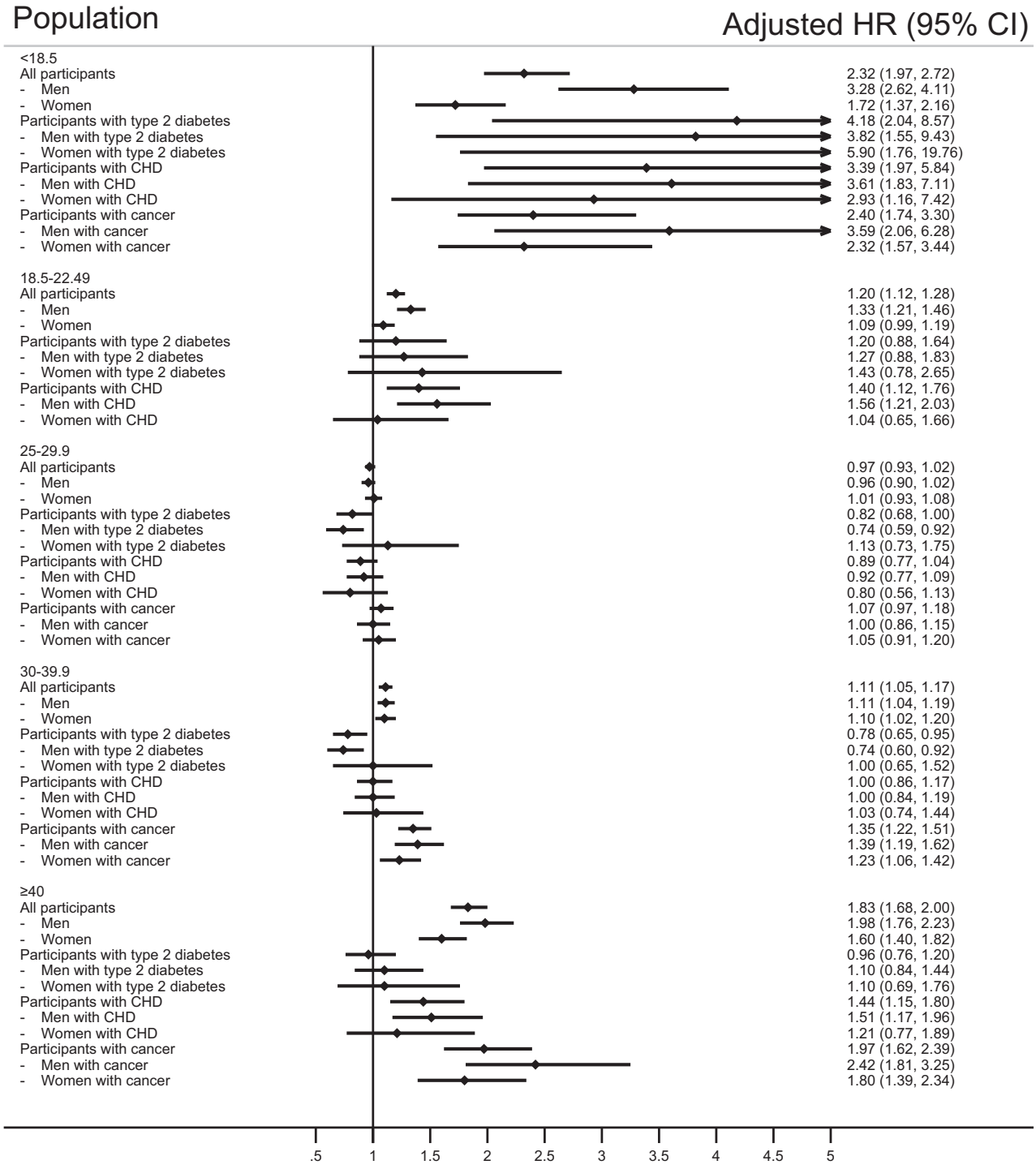

Figure 1—Adjusted HRs (95% CIs) for all-cause mortality in relation to BMI categories at baseline, with BMI 22.5–24.9 kg/m^2 as reference.

In smokers and previous smokers with type 2 diabetes, cancer, or CHD, obese (or overweight) participants had lower mortality than normal weight participants. However, in current smokers, the association with lower mortality was more pronounced and included those with higher BMI values. In never smokers with cancer, no evidence was observed of an obesity paradox. Other important confounding factors in the data were age, ethnicity, and renal and heart failure (Supplementary Table 2).

Relationships Between Continuous BMI and Cause-Specific Mortality

Similar relationships were observed when considering death as a result of cancer and other causes (Supplementary Figs. 4 and 6). For cardiovascular death, some subgroups (all participants, women only, smokers with diabetes) showed similar results to those of the BMI-all cause mortality analysis, but differences were observed in other subgroups (Supplementary Fig. 5). The obesity paradox did not appear to be present in these

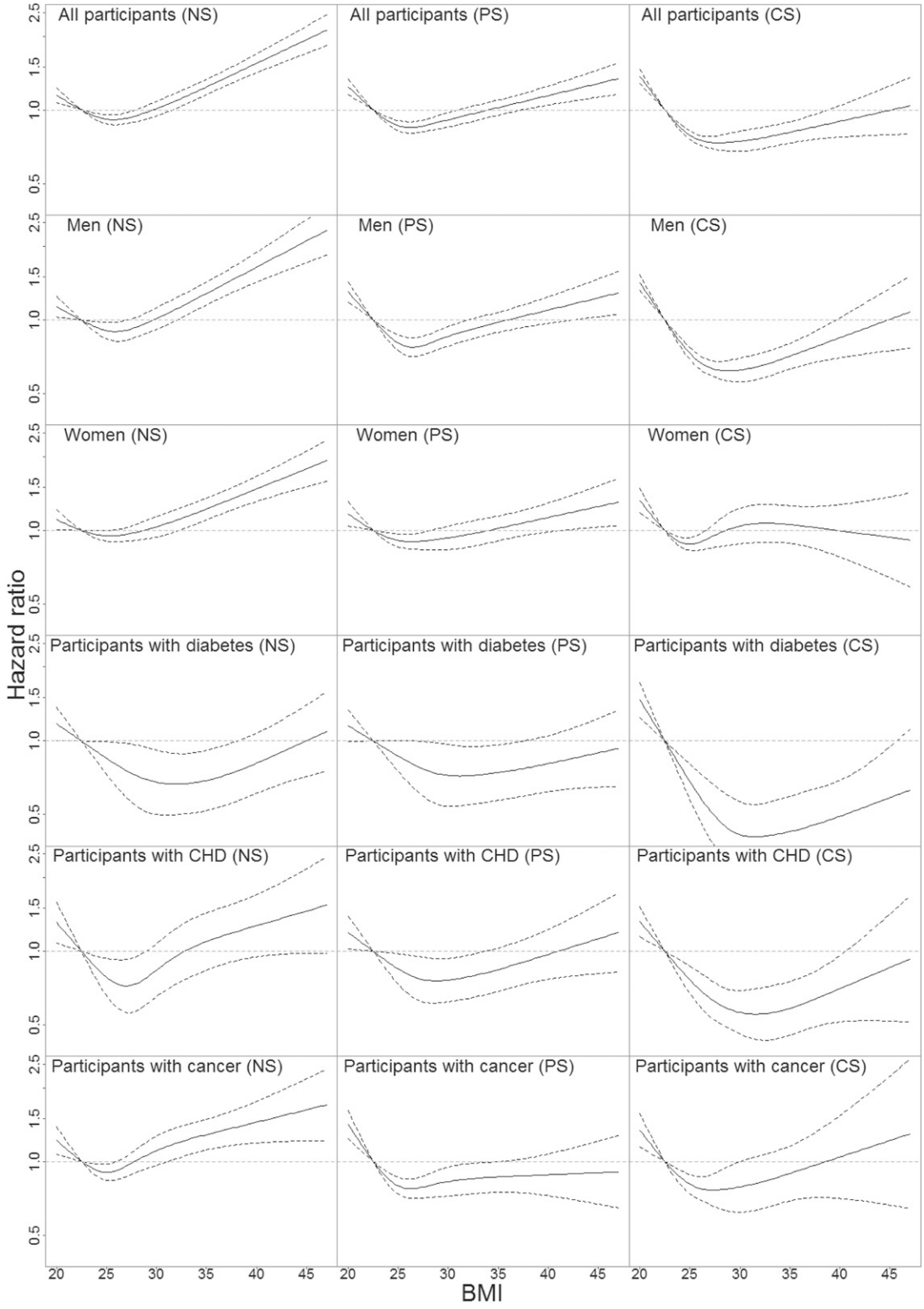

Figure 2—Adjusted HRs (95% CIs) for all-cause mortality associated with BMI by smoking status in men and women and by CHD, type 2 diabetes, and cancer status at baseline, with BMI = 22.5 kg/m^2 as reference. Models are adjusted for age, smoking status (current, past, never), ethnicity, education, deprivation index, and chronic diseases diagnosed before study entry. CS, current smoker; NS, never smoker; PS, previous smoker.

other subgroups, and although smoking still seemed to modify the relationship, it was not as influential as observed in the all-cause mortality analysis and other cause-specific mortality analyses. Larger CIs also were observed in the cardiovascular mortality results as a result of lower event rates or larger heterogeneity.

Body Fat Percentage and All-Cause Mortality

In keeping with the BMI results, we observed U-shaped relationships between

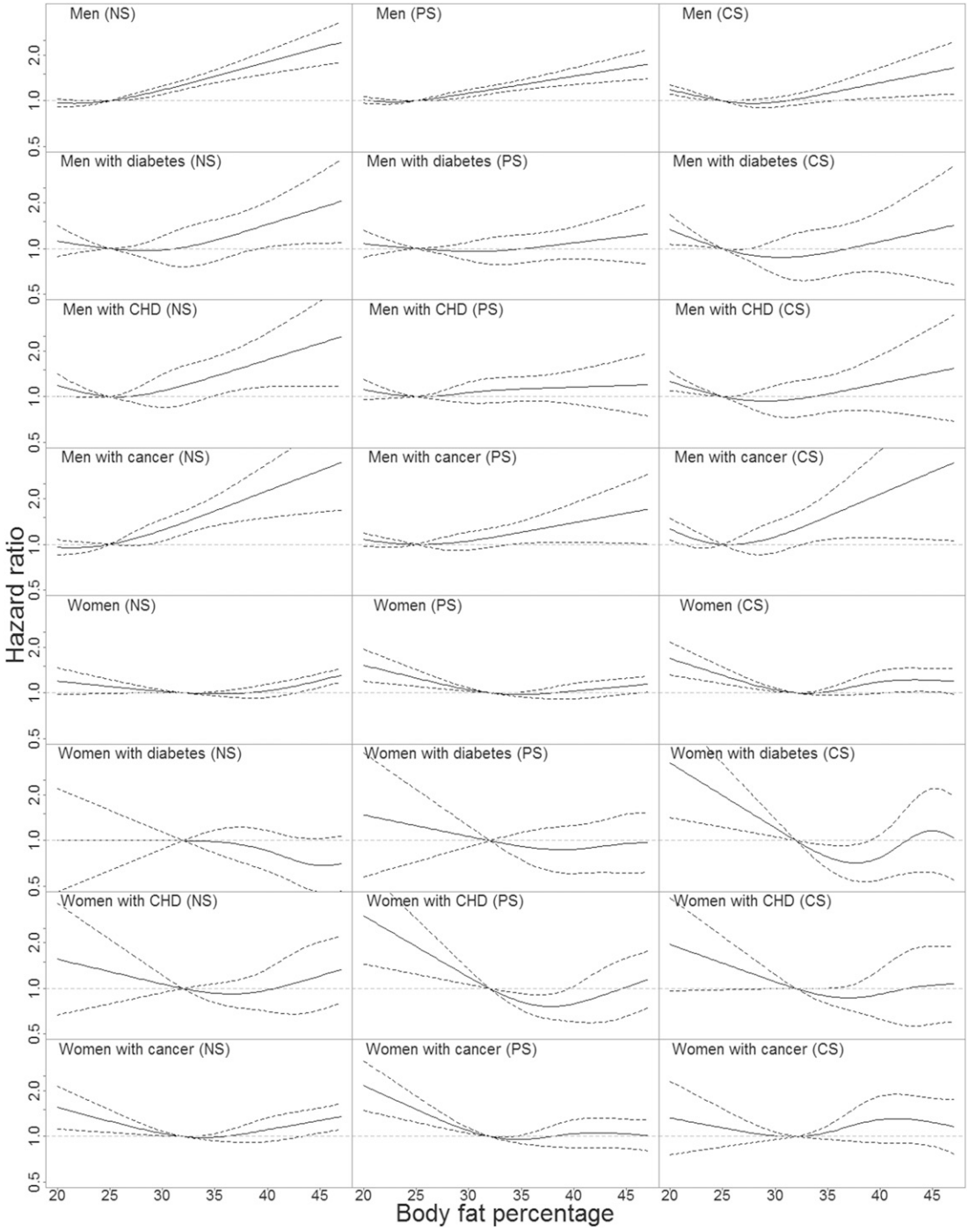

Figure 3—Adjusted HRs (95% CIs) for all-cause mortality associated with body fat percentage by smoking status in men and women and by CHD, type 2 diabetes, and cancer status at baseline, with BMI = 22.5 kg/m^2 as reference. Models are adjusted for age, smoking status (current, past, never), ethnicity, education, deprivation index, and chronic diseases diagnosed before study entry. CS, current smoker; NS, never smoker; PS, previous smoker.

body fat percentage and mortality. Among all participants and subgroups with type 2 diabetes or CHD, low (<20%) and very high (>45%) body fat were significantly associated with higher mortality, except in women with type 2 diabetes and CHD in whom some high body fat values were not associated with a different mortality than those with a normal body fat value (32%). However, for current smokers, only the subgroups of all men and men with prior cancer showed a significant increase in mortality for very high body fat percentages (Fig. 3).

The body fat percentage associated with the minimum mortality in men and women was 24.5% and 36.1%, respectively. In men with type 2 diabetes, CHD, or cancer, the minimum mortality was associated with numerically higher percent body fat values (type 2 diabetes 29.2%, CHD 27.7%, cancer 25.2%) than in the whole male subgroup, but these risks were not significantly lower than the risk associated with the reference value of 25%. In women with type 2 diabetes, CHD, or cancer, the minimum mortality

risk was associated with higher percent body fat values (type 2 diabetes 44.3%, CHD 39.5%, cancer 37%) than in the whole female subgroup, and only in women with type 2 diabetes were these values not associated with a lower mortality compared with the reference value of 32%.

Waist Circumference and All-Cause Mortality Risk

Similar U-shaped relationships were observed between waist circumference and mortality (Supplementary Fig. 2). However, the paradox was only observed in men with CHD. In all women and in women with CHD, a high but not a low waist circumference value was associated with a higher mortality than the reference value of 85 cm. In women with type 2 diabetes, mortality did not significantly vary by waist circumference compared with the referent group.

WHR and All-Cause Mortality Risk

Only men with CHD had similar adiposity and mortality relationships as seen with the previous adiposity measures (Supplementary Fig. 3). In men with type 2 diabetes, there was a suggestion of a U-shaped relationship, but only high WHR in previous smokers and low WHR in current smokers were significantly associated with higher mortality compared with reference values.

For men and women in the all participants group, relationships between WHR and mortality risk were positive and demonstrated a more linear relationship (Supplementary Fig. 3). In women with type 2 diabetes, cancer, or CHD, those with low WHR values had a similar mortality risk to those with reference values. In women with CHD, high WHR values were associated with a higher mortality risk than the referent group, but this was only observed in current and past smokers. In women with type 2 diabetes, cancer, and CHD but who never smoked, mortality risks were not statistically different than the referent groups.

Sensitivity Analyses

We performed several sensitivity analyses. First, analyzing categorical BMI according to the WHO categories only and not further splitting the 18.5–24.9 kg/m^2 category had some small effect on the results (data not shown). In men, being obese was no longer associated with higher mortality than the referent group (BMI 18.5–24.9 kg/m^2), and being overweight was associated with lower mortality. The only other observed differences were in the overweight categories, where some of the subgroups (all participants, participants with type 2 diabetes, participants with CHD, and men with CHD) were now observed to have a statistically significant lower mortality than the referent group. For all other subgroups, the WHO categorization did not affect the results. Second, exclusion of participants who died within 1 year of study entry did not substantively alter the conclusions. Finally, when we excluded participants with type 2 diabetes, CHD, or cancer from the whole population, the results and conclusions did not differ substantively from the original analyses (data not shown).

CONCLUSIONS

Main Findings

This large cohort study provides several original observations. First, even after adjusting for several potential confounders, the relationship between BMI and mortality was U-shaped, with a minimum risk for mortality in the overweight range (BMI 27.2 kg/m^2). Second, the obesity paradox was observed in men and women with type 2 diabetes, with the minimum mortality risk in the obese range (women with type 2 diabetes 34.1 kg/m^2, men with type 2 diabetes 31.7 kg/m^2), whereas in men and women with CHD, the minimum risk was in the overweight range. Third, smoking exaggerated the U-shaped relationship between BMI and mortality by increasing the relative risk in normal weight and underweight participants compared with overweight and obese participants, as previously described in CHD (20). Finally, U-shaped relationships between measures of adiposity and mortality were less apparent on the basis of body fat percentage, waist circumference, and WHR, but the influence of smoking on these relationships was similar to that seen in BMI-mortality relationships.

Previous Studies

Several other studies in diabetes and CHD cohorts have observed the obesity paradox. Most of these only consider a single disease subgroup, such as diabetes. Only the French E3N (Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale) EPIC (European Prospective Investigation into Cancer and Nutrition) study (20) and the study by Badrick et al. (9) analyzed the obesity paradox in subgroups with and without diabetes. Both studies identified the obesity paradox, and Badrick et al. found that smoking as an effect modifier explained the paradox (P for interaction = 0.009). For example, the HR (95% CI) for mortality associated with BMI values 30–35 kg/m^2 in smokers with diabetes was 0.72 (0.56, 0.92) compared with normal weight participants. These articles, however, had limited sample sizes and did not use other measures of adiposity apart from BMI. For example, Badrick et al. studied only 1,795 smokers with diabetes.

In type 2 diabetes, the Look AHEAD (Action for Health in Diabetes) trial (21) did not show cardiovascular disease or mortality benefits through weight loss (22). Observational studies of intentional weight loss have provided conflicting results and can be prone to bias. For example, a study in people with type 2 diabetes (23,24) suggested that intentional weight loss is associated with increased mortality compared with individuals with stable weight, but the influence of reverse causality from diseases that cause pathological weight loss is difficult to exclude. Other observational studies (25) in type 2 diabetes and in the general population have suggested mortality benefits through intentional weight loss.

Bowman et al. (25) showed that having a large waist circumference and being normal weight or overweight (defined by BMI) is associated with substantial excess mortality. Although their study involved UK Biobank participants, it focused on the interaction between WHR and BMI on mortality, and it was limited by considering BMI only as a categorical variable, studying participants aged 60–69 years, and having a sample size of 130,473.

The EPIC cohort (20,26) was the largest study to explore the obesity paradox in a general population of 359,387 participants through multiple measures of adiposity and found that both BMI and central adiposity measures are associated with mortality risk. The EPIC study had limited data on individuals with BMI $>$35 kg/m^2, and it only included healthy individuals after excluding those with a history of cancer, heart disease, or stroke.

Mechanistic Insights

BMI, as a construct, is limited because it conflates lean mass and fat mass. Individuals with low BMI generally will have a low fat mass, which might be expected to have some health advantages. However, low BMI also is linked to low muscle mass, which could be a marker of serious underlying disease and frailty. Similarly, some fit and healthy individuals with a high BMI have high muscle mass and low fat mass. As such, BMI is an imperfect proxy for adiposity.

In the current analysis, smoking significantly influenced the shape of relationships between BMI and mortality such that among smokers, individuals with low BMI appeared to have higher mortality than overweight and obese individuals. Although this relationship persisted after adjusting for the presence of known disease, undiagnosed serious smoking-related diseases, such as chronic obstructive pulmonary disease and lung cancer, could partly explain the obesity paradox through confounding and reverse causation.

Our assessment of body fat shows the individual contribution of low body fat to mortality. The U-shaped relationships observed suggest that low body fat per se generally is associated with higher mortality than normal or high body fat. Although we adjusted for several important confounders, the analysis could not differentiate between the presence of a genuine causal relationship between low body fat and higher mortality and the influence of residual confounding from unmeasured variables.

The strongest evidence for the obesity paradox we observed is in participants with type 2 diabetes. A plausible explanation is that people with type 2 diabetes have a higher likelihood of being obese than other groups (27). In these people, chronic illness leading to weight loss (which is linked to higher mortality) would have a greater tendency to lead to a BMI reduction into the normal range rather than into the underweight range, which would be a more likely scenario in the general population. Prospective cohort studies comparing BMI changes during terminal illnesses in people with and without diabetes could test this hypothesis.

Strengths and Limitations

This study had several strengths. First, it involved a large prospective cohort with high-quality baseline data on several potential confounders in the relationship between BMI and mortality. Second, we considered several adiposity measures (BMI, body fat percentage, waist circumference, and WHR) that enabled us to separate relationships of lean mass and fat mass with mortality risk. Third, we considered BMI as both a categorical exposure variable and a continuous variable, which enabled us to establish cohort-specific adiposity values associated with the lowest mortality risks. Fourth, we assessed relationships in the whole cohort in addition to the subgroups in which the obesity paradox has been described previously (i.e., CHD, cancer, type 2 diabetes). Finally, objectively measured body weight and body fat were used, which are less prone to error than questionnaire-based self-report.

We also acknowledge some limitations. First, although we adjusted for many variables to minimize the potential for cofounding, we cannot rule out the role of unmeasured confounders. Confounding also can be amplified by collider stratification bias where obesity itself is a risk factor for the incident disease (13). Second, UK Biobank participants comprise a relatively healthy cohort and may not be fully representative of the U.K. population (28). Third, although the data were rich, all exposures and confounders were assessed at baseline only; therefore, adiposity levels assessed after diagnosis of a disease, such as diabetes, may have been influenced by the effects of that disease and/or clinical interventions. Fourth, all participants were from the U.K. and were middle-aged or elderly, so extrapolation of findings to other cohorts should be done with caution (29). Finally, although participant numbers were large, disease subgroups (type 2 diabetes and CHD) were smaller, leading to larger CIs and lower statistical power, particularly in women.

Clinical Implications

These observational data confirm prior research findings (27) and provide further mechanistic insights but cannot provide clinical guidance regarding the potential risks or benefits of weight loss in the general population or in diseased groups. Such clinical guidance only can come from randomized controlled trials.

Conclusion

Even after adjusting for potential confounders, strong U-shaped relationships were observed between several measures of adiposity and mortality risk. We showed strong evidence of the obesity paradox in individuals with type 2 diabetes and that smoking modifies relationships between BMI and mortality. Body fat percentage and waist circumference analyses also demonstrated U-shaped relationships with mortality risk but did not show evidence of an obesity paradox. These data provide further insight into the potential mechanisms that link adiposity and mortality and deepen our understanding of the obesity paradox. However, more research is required to understand the true causal nature of these relationships before clinical guidance is modified.

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