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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Abbreviations

BMI: Body mass index

OP: Obesity paradox

CHD: Coronary heart disease

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 a genuine clinical benefit of excess body weight. We aimed to gain deeper insights in the paradox through: analysing mortality relationships with several adiposity measures; assessing subgroups with type 2 diabetes, coronary heart disease (CHD) and smokers and by adjusting for several confounders.

Research design and methods

We studied the general UK Biobank population (n=502,631), along with 3 subgroups: individuals with a) type 2 diabetes (n=23,842); CHD (n=24,268) and c) cancer (n=45790) 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, education and disease history.

Results

For BMI, the obesity paradox was observed among people with type 2 diabetes (adjusted HR: obese vs. normal BMI: 0.78, 95% CI: 0.65,0.95), but not among those with CHD (HR: 1.00: 0.86,1.17). The obesity paradox was pronounced in current smokers, absent in never

smokers, and more pronounced in men than women. For other adiposity measures, there was less evidence for an obesity paradox, yet smoking status consistently modified the adiposity-mortality relationships.

Conclusions

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

Introduction

The 'obesity paradox' refers to the commonly observed epidemiological finding that being overweight (body mass index (BMI) 25 to <30 kg/m^2) or obese (BMI ≥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 type 2 diabetes[8–10], among many others. 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 bodyweight, is of clear clinical importance.

The obesity paradox has been extensively explored with regards 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 using the 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.

Methods

Study and disease subgroups

The UK Biobank recruited 502,631 participants over the age of 40 years between 2006 and 2010. All participants provided health, lifestyle and sociodemographic data through questionnaires and interviews, underwent 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 registers, have been linked to UK Biobank.

We studied the whole Biobank cohort and three subgroups. These subgroups were individuals with: i) type 2 diabetes defined using a validated algorithm[16]; ii) CHD, defined as participants with angina, myocardial infarction, coronary angioplasty/stent or coronary artery bypass surgery prior to recruitment; iii) cancer, as diagnosed in the cancer registry prior to UK Biobank assessment centre 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 score was calculated from postcode based on national census data. Incident cancer and all-cause mortality information were obtained from national registers linked to UK Biobank.

BMI, calculated as weight (kg) divided by height (m) squared, was analysed both as a continuous variable, with a reference value of 22.5 kg/m^2, and as a categorical variable based on the World Health Organisation (WHO) classifications where we split the 18.5 to 25 category into two groups, as in previous literature[9,17]; categories: BMI <18.5, 18.5 to 22.4, 22.5 to 24.9 (reference), 25.0 to 29.9, 30.0 to 39.9 and ≥40.0 kg/m^2.

Body fat percentage was estimated using 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 80cm and 0.85 respectively, and for men were 94cm and 0.9 respectively, based on the WHO classification and recommendations[18].

Smoking status was defined as a categorical variable with 4 categories: current smokers, past smokers, never smokers and unknown.

Deaths were identified from the death register linked to the UK Biobank data; ICD10 codes being used to identify the primary cause of death. Cancer deaths were defined as ICD10 codes C00-C97 and cardiovascular deaths as I00-I99, E10.5, E11.5, E12.5, E13.5 or E14.5. Deaths with other ICD10 codes as the primary cause of death were labelled as death for other causes.

Statistical analyses

The exposure was adiposity, assessed as BMI, body fat, waist circumference or WHR and the outcome was all-cause mortality.

Survival analysis was conducted in the whole Biobank cohort and in diabetes, CHD and cancer subgroups separately, then further stratified by smoking (using the categories current, past and never smokers).

We used Cox proportional hazard regression models with age as the timescale, left truncated at study entry, and the outcome was age at death recorded by the death register. 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 one 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 non-linear (e.g J-shape) relationships. Non-linearity 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 using: 1) unadjusted models; and 2) 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 BMI value with the smallest hazard ratio, with bootstrapped confidence intervals.

We considered the obesity paradox to be present in a cohort if a BMI value greater than 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 was also tested by including a smoking interaction with adiposity.

Data analysis was performed using STATA (*Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP) and R (version 3.4.2). $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

The final cohort comprised 229,170 men and 273,461 women. A total of 212,166 individuals (42%) were overweight, of which 47% are 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 (BMI<18.5 kg/m^2) compared with 10% among the obese individuals. Data on BMI, %body fat, waist circumference and WHR were available in 99%, 98%, 99% and 99% of participants respectively.

A total of 13,502 (56.6%) of the 23,842 individuals with type 2 diabetes and 9,704 (40%) of the 24,268 individuals with CHD were obese. 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 those 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% (8,286) and 20.8% (2,998) of all deaths, respectively.

Relationships between BMI categories and mortality

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

Morbidly obese individuals (>= 40 kg/m2) had higher mortality than normal weight in the overall population, but not in the type 2 diabetes or women with CHD subgroups.

In people with type 2 diabetes, being obese was associated with lower mortality than being normal weight (HR: 0.78 [CI, 0.65 to 0.95]), and this appeared to be driven by a lower hazard in men with type 2 diabetes (HR: 0.74 [CI, 0.60 to 0.92]), while women with type 2 diabetes did not have a statistically lower mortality risk (HR: 1.13 [CI, 0.73 to 0.1.75]). Hence, in the categorical analyses the obesity paradox was present only in men with type 2 diabetes.

Compared with normal-weight individuals, being overweight was associated with a lower mortality risk only in men with type 2 diabetes (HR: 0.74 [CI, 0.59 to 0.92]).

Relationships 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 (Figure 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 [CI, 0.80 to 0.86]; referent BMI: 22.5 kg/m^2; supplementary table ST1), whereas among individuals 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, lowest mortality rates were observed at 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 non-smokers (p-interaction: 0.002; figure 3). The paradox was still present in men who had previously smoked, but to a lesser extent than the current smokers. In particular, obese smokers had lower mortality than normal-weight smokers. In contrast, obese non-smokers had higher mortality than normal-weight non-smokers and only those in the overweight range had lower mortality. In all women, however, there was no evidence of the obesity paradox.

In smokers and ex-smokers with type 2 diabetes, cancer or CHD, obese (or overweight) individuals had lower mortality than normal weight individuals. However, in current smokers the association with lower mortality was more pronounced and included those with higher BMI values. In never smokers with cancer, there was no evidence of an obesity paradox. Other important confounding factors in the data included: age, ethnicity and renal and heart failure (see supplementary table ST2).

Relationships between continuous BMI and cause specific mortality

Similar relationships were observed when considering death by cancer and death from other causes (supplementary figures SF4 and SF6). For cardiovascular death, some sub-groups (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 sub-groups (supplementary figure SF5). The obesity paradox did not appear to be present in these other sub-groups and although smoking still appeared to modify the relationship, it was not as influential as observed in the all-cause mortality analysis and other cause-specific mortality

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

The percentage body fat 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 percentage body fat value of 25%. In women with type 2 diabetes, CHD or cancer, the minimum mortality risk was associated with higher percentage 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 to the reference value of 32%.

Waist circumference and all-cause mortality risk

Similar U-shaped relationships were observed between waist circumference and mortality (supplementary figure SF2). However, the paradox was only observed in men with CHD. In all women, and in women with CHD, high waist, but not low waist circumference, was associated with a higher mortality than the reference value (85cm). In women with type

2 diabetes, mortality did not significantly vary by waist circumference when compared with the referent group.

Waist-to-hip ratio (WHR) and all-cause mortality risk

Only men with CHD had similar adiposity and mortality relationships as seen with the previous adiposity measures (supplementary figure SF3). In men with type 2 diabetes, there was a suggestion of a U-shaped relationship but only high WHR values were significantly associated with higher mortality compared to reference values in previous smokers.

For men and women in the 'all participants' group, relationships between WHR and mortality risk were positive and demonstrated a more linear relationship (supplementary figure S3). In women with type 2 diabetes, cancer or CHD, individuals with low WHR values had a similar mortality risk to women with reference values. In women with CHD, high WHR values were associated with a higher mortality risk than referent, but this was only observed in the current and past smokers. In women with type 2 diabetes, cancer and never smokers with CHD, mortality risks were not statistically different to referent.

Sensitivity analyses

We performed several sensitivity analyses: 1) Analysing categorical BMI according to the WHO categories only, and not further splitting the 18.5-25 category, had some small effect on our results (data not shown). In men, being obese was no longer associated with higher mortality than the reference group (BMI: 18.5-24.9) and being overweight was associated with lower mortality than the reference. 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 significantly lower mortality than the reference group. For all other subgroups, the WHO categorisation did not affect our results. 2) Excluding patients who died within one year of study entry did not substantively alter our conclusions. 3) When we excluded patients with type 2 diabetes, CHD, or cancer, from the whole population, our results and conclusions did not differ substantively from the original analyses (data not shown).

Discussion

Main findings

This large cohort study provides several original observations: 1), 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); 2) 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; 3) smoking exaggerated the U-shaped relationship between BMI and mortality by increasing the relative risk in normal-weight and underweight individuals compared to overweight and obese participants - as previously described in CHD[20]; 4) U-shaped relationships between measures of adiposity and mortality were less apparent using body fat percentage, waist circumference and waist-hip ratios 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 those with diabetes. Only the French E3N EPIC study[20] and the study by Badrick et al[9] analysed the obesity paradox in subgroups with and without diabetes. Both studies identified the obesity paradox and Badrick et al found that that smoking as an effect modifier explained the paradox (p-interaction: p=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 to 0.92) compared with normal weight participants[9]. These papers were, however, limited in sample size and did not use any other measure of adiposity apart from BMI. For example, Badrick et al studied only 1795 smokers with diabetes[9].

In type 2 diabetes, the look AHEAD trial[21] did not show CVD 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 was associated with increased mortality compared with stable weight individuals, but the influence of reverse causality from diseases causing 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.

Bownam et al showed that having a high waist circumference and being normal weight or overweight (defined by BMI) was associated with substantial excess mortality[25]. Although Bowman's study involved UK Biobank participants, it focussed 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 using multiple measures of adiposity and found both BMI and central adiposity measures were both 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 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 will generally have a low fat mass which might be expected to have some health advantages. However, low BMI is also linked to low muscle mass which could be a marker of serious underlying disease and frailty. Similarly, there will be some fit and healthy individuals with high BMI who have high muscle mass and low fat mass. As such, BMI is an imperfect proxy for adiposity.

In our 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 enabled us to assess the individual contribution of low body fat to mortality. The U-shaped relationships observed suggest that low body fat *per se* is generally associated with higher mortality than individuals with normal or higher body fat percentage. Although we adjusted for several important confounders, our analysis is unable to 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.

We observed strongest evidence for the obesity paradox in participants with type 2 diabetes. A plausible explanation for this is that participants with type 2 diabetes would have a higher likelihood of being obese than other groups[27]. In these people, weight-losing chronic illness (linked to higher mortality), would have a greater tendency to lead to a BMI reduction into the normal BMI range rather than into the underweight BMI 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

Our study has several strengths: 1) it involved a large prospective cohort with high-quality baseline including data on several potential confounders in the relationship between BMI and mortality; 2) we considered several adiposity measures (BMI, %fat mass, waist circumference and waist-hip ratio) which enabled us to separate relationships of lean mass and fat mass with mortality risk; 3) we considered BMI as a categorical exposure and as a continuous variable which enabled us to establish cohort-specific adiposity values associated with the lowest mortality risks; 4) we assessed relationships in the whole cohort in addition to three groups in which the obesity paradox has been described previously (those with CHD,

cancer and type 2 diabetes); 5)Objectively measured body weight and body fat were used, which are less error prone than questionnaire-based self-reports.

We acknowledge some limitations: 1) although we adjusted for many variables that minimised the potential for cofounding, we cannot rule out the role of unmeasured confounders. Confounding can also be amplified by collider stratification bias where obesity is itself a risk factor for the incident disease[13]; 2) UK Biobank participants are a relatively healthy cohort and may not be fully representative of the UK population[28]; 3) 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; 4) all participants were UK-based, middle-aged or elderly and so extrapolation of findings to different cohorts should be done with a degree of caution[29]; 5) although participant numbers were high, disease subgroups (type 2 diabetes and CHD) were smaller, leading to larger confidence intervals 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 can only come from randomised controlled trials.

Conclusion

Even after adjusting for potential confounders, there were strong U-shaped relationships 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. Analysis using body fat percentage and waist circumference also demonstrated U-shaped relationships with mortality risk, but did not show evidence of an obesity paradox. These data provide further insights into potential mechanisms linking adi-

posity and mortality, and deepen our understanding of the obesity paradox. However, further research is required to understand the true causal nature of these relationships before clinical guidance is modified.

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Author contributions

D.A.J. conducted the analysis, researched data, wrote the manuscript and contributed to the discussion. H.A.R. contributed to the discussion and reviewed/edited the manuscript. J.B. contributed to the discussion and reviewed/edited the manuscript. R.L. contributed to the discussion and reviewed/edited the manuscript. N.S. contributed to the discussion and reviewed/edited the manuscript. M.S. provided statistical support, contributed to the discussion and reviewed/edited the manuscript. M.R. provided clinical knowledge, contributed to the discussion and reviewed/edited the manuscript.

Guarantor’s statement

David A Jenkins is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of conflicts of interest

The authors declare that they have no conflicts of interest relating to the publication of this work.

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Table 1

	BMI categories					
Characteristics	**<18.5**	**18.5-22.49**	**22.5-24.9**	**25-29.9**	**30-39.9**	**>40**
No of participants	2626 (0.52)	59538 (11.85)	102909 (20.47)	212166 (42.21)	112581 (22.4)	12811 (2.55)
Female	2079 (79.17)	43980 (73.87)	61709 (59.96)	99904 (47.09)	57682 (51.24)	8107 (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	2438 (92.84)	56372 (94.68)	97516 (94.76)	200043 (94.29)	105354 (93.58)	11091 (86.57)
South Asian	44 (1.68)	808 (1.36)	1661 (1.61)	3543 (1.67)	1666 (1.48)	345 (2.69)
African Caribbean	10 (0.38)	453 (0.76)	1042 (1.01)	3257 (1.54)	2777 (2.47)	526 (4.11)
Mixed or other	112 (4.27)	1657 (2.78)	2272 (2.21)	4342 (2.05)	2160 (1.92)	364 (2.84)
Deprivation *	-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	1059 (40.33)	25105 (42.17)	38668 (37.57)	65967 (31.09)	27561 (24.48)	2845 (22.21)
Smoking						
Never	1474 (56.13)	35883 (60.27)	59747 (58.06)	113066 (53.29)	56883 (50.53)	6543 (51.07)
Previous	540 (20.56)	15923 (26.74)	31893 (30.99)	76322 (35.97)	43994 (39.08)	4422 (34.52)
Current	598 (22.77)	7529 (12.65)	10842 (10.54)	21693 (10.22)	10969 (9.74)	1358 (10.6)
Chronic diseases						
Hyperlipidemia	11 (0.42)	263 (0.44)	765 (0.74)	2788 (1.31)	2412 (2.14)	331 (2.58)
Renal failure	47 (1.79)	386 (0.64)	715 (0.69)	2187 (1.03)	2041 (1.81)	478 (3.73)
Liver failure	4 (0.15)	35 (0.06)	56 (0.05)	143 (0.07)	116 (0.1)	7 (0.05)
Heart failure	47 (1.79)	432 (0.73)	824 (0.8)	2633 (1.24)	2589 (2.3)	574 (4.48)
Dementia	8 (0.3)	125 (0.21)	212 (0.21)	473 (0.22)	292 (0.26)	51 (0.4)
Cancer	306 (11.7)	5806 (9.75)	9657 (9.38)	18827 (8.87)	10066 (8.94)	1128 (8.8)
Diabetes	29 (1.1)	573 (0.96)	1745 (1.7)	7993 (3.77)	11146 (9.9)	2356 (18.39)
CHD	55 (2.09)	1128 (1.89)	2898 (2.82)	10483 (4.94)	8621 (7.66)	1083 (8.45)

Values are numbers and percentage unless otherwise stated

* Values are mean (SD)

Table and figure legends

Table 1: Baseline characteristics by BMI category

Figure 1: Adjusted hazard ratios (95% CI) for all-cause mortality in relation to BMI categories at baseline with BMI 22.5-24.9 as referent

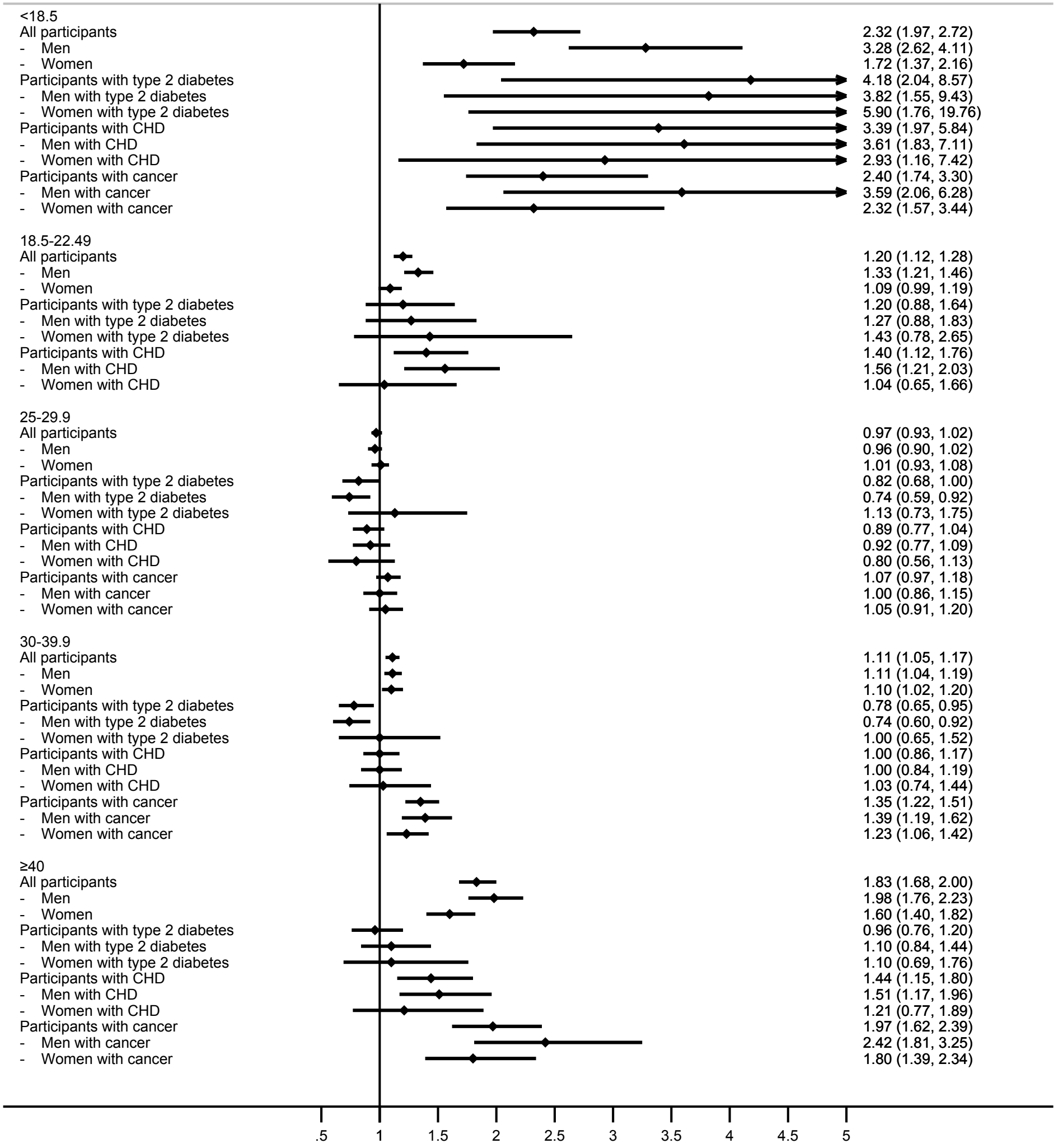
Figure 2: Adjusted hazard ratios (95% CI) for all-cause mortality associated with BMI by smoking status (never smokers = NS, previous smoker = PS and current smokers = CS) in men and women and by CHD, type 2 diabetes and cancer status at baseline with BMI 22.5 as referent*

* Models are adjusted for, age, smoking status (current, past and never), ethnicity, education, deprivation index and chronic diseases diagnosed before study entry

Figure 3: Adjusted hazard ratios (95% CI) for all-cause mortality associated with body fat percentage by smoking status (never smokers = NS, previous smoker = PS and current smokers = CS) in men and women and by CHD, type 2 diabetes and cancer status at baseline with BMI 22.5 as referent*

* Models are adjusted for, age, smoking status (current, past and never), ethnicity, education, deprivation index and chronic diseases diagnosed before study entry

Population	Adjusted HR (95% CI)
<18.5	
All participants	2.32 (1.97, 2.72)
- Men	3.28 (2.62, 4.11)
- Women	1.72 (1.37, 2.16)
Participants with type 2 diabetes	4.18 (2.04, 8.57)
- Men with type 2 diabetes	3.82 (1.55, 9.43)
- Women with type 2 diabetes	5.90 (1.76, 19.76)
Participants with CHD	3.39 (1.97, 5.84)
- Men with CHD	3.61 (1.83, 7.11)
- Women with CHD	2.93 (1.16, 7.42)
Participants with cancer	2.40 (1.74, 3.30)
- Men with cancer	3.59 (2.06, 6.28)
- Women with cancer	2.32 (1.57, 3.44)
18.5-22.49	
All participants	1.20 (1.12, 1.28)
- Men	1.33 (1.21, 1.46)
- Women	1.09 (0.99, 1.19)
Participants with type 2 diabetes	1.20 (0.88, 1.64)
- Men with type 2 diabetes	1.27 (0.88, 1.83)
- Women with type 2 diabetes	1.43 (0.78, 2.65)
Participants with CHD	1.40 (1.12, 1.76)
- Men with CHD	1.56 (1.21, 2.03)
- Women with CHD	1.04 (0.65, 1.66)
25-29.9	
All participants	0.97 (0.93, 1.02)
- Men	0.96 (0.90, 1.02)
- Women	1.01 (0.93, 1.08)
Participants with type 2 diabetes	0.82 (0.68, 1.00)
- Men with type 2 diabetes	0.74 (0.59, 0.92)
- Women with type 2 diabetes	1.13 (0.73, 1.75)
Participants with CHD	0.89 (0.77, 1.04)
- Men with CHD	0.92 (0.77, 1.09)
- Women with CHD	0.80 (0.56, 1.13)
Participants with cancer	1.07 (0.97, 1.18)
- Men with cancer	1.00 (0.86, 1.15)
- Women with cancer	1.05 (0.91, 1.20)
30-39.9	
All participants	1.11 (1.05, 1.17)
- Men	1.11 (1.04, 1.19)
- Women	1.10 (1.02, 1.20)
Participants with type 2 diabetes	0.78 (0.65, 0.95)
- Men with type 2 diabetes	0.74 (0.60, 0.92)
- Women with type 2 diabetes	1.00 (0.65, 1.52)
Participants with CHD	1.00 (0.86, 1.17)
- Men with CHD	1.00 (0.84, 1.19)
- Women with CHD	1.03 (0.74, 1.44)
Participants with cancer	1.35 (1.22, 1.51)
- Men with cancer	1.39 (1.19, 1.62)
- Women with cancer	1.23 (1.06, 1.42)
≥40	
All participants	1.83 (1.68, 2.00)
- Men	1.98 (1.76, 2.23)
- Women	1.60 (1.40, 1.82)
Participants with type 2 diabetes	0.96 (0.76, 1.20)
- Men with type 2 diabetes	1.10 (0.84, 1.44)
- Women with type 2 diabetes	1.10 (0.69, 1.76)
Participants with CHD	1.44 (1.15, 1.80)
- Men with CHD	1.51 (1.17, 1.96)
- Women with CHD	1.21 (0.77, 1.89)
Participants with cancer	1.97 (1.62, 2.39)
- Men with cancer	2.42 (1.81, 3.25)
- Women with cancer	1.80 (1.39, 2.34)



All participants (NS)
All participants (PS)
All participants (CS)
Men (NS)
Men (PS)
Men (CS)
Women (NS)
Women (PS)
Women (CS)
Participants with diabetes (NS)
Participants with diabetes (PS)
Participants with diabetes (CS)
Participants with CHD (NS)
Participants with CHD (PS)
Participants with CHD (CS)
Participants with cancer (NS)
Participants with cancer (PS)
Participants with cancer (CS)
Hazard ratio
0.5
1.0
1.5
2.5
20
25
30
35
40
45
BMI

Men (NS)
Men (PS)
Men (CS)
Men with diabetes (NS)
Men with diabetes (PS)
Men with diabetes (CS)
Men with CHD (NS)
Men with CHD (PS)
Men with CHD (CS)
Men with cancer (NS)
Men with cancer (PS)
Men with cancer (CS)
Women (NS)
Women (PS)
Women (CS)
Women with diabetes (NS)
Women with diabetes (PS)
Women with diabetes (CS)
Women with CHD (NS)
Women with CHD (PS)
Women with CHD (CS)
Women with cancer (NS)
Women with cancer (PS)
Women with cancer (CS)

Hazard ratio

0.5
1.0
2.0

20
25
30
35
40
45

Body fat percentage