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Body composition and mortality from middle to old age: a prospective cohort study from the UK Biobank

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Competing Interests statement

The authors have nothing to disclose.

Abstract

Background: How the association between adiposity and the risk of death changes with age, and which is the optimal level of adiposity to reduce mortality in older ages, is still not completely understood. We aimed to ascertain the age-specific risks of mortality associated with different measures of adiposity.

Methods: This was a prospective UK Biobank cohort study. Participants were categorized based on five different adiposity and body composition metrics. We explored the age-varying associations between body composition indices and all-cause mortality from 45 to 85 years of age at follow-up using hazard ratios (HR) from flexible parametric survival models with multivariable adjustment and age as timescale. Participants were followed from baseline (2006-2010) through 31 March 2020.

Results: We included 369 752 participants (mean baseline age = 56.3 ± 8.1 years; range 38.9 to 73.7 years; 54.1% women) and 10,660 deaths during a median follow-up of 11.4 years. Associations between body mass index and mortality were similar when using the fat mass index in magnitude and shape. Compared to participants with normal weight, overweight was not associated with the risk of death regardless of age and the adiposity measure used. Participants with obesity class I showed a HR of 1.20 (95% confidence interval [CI]: 1.08, 1.33) and 1.14 (95%CI: 0.98, 1.30) at ages 60 and 80, respectively, and participants with obesity class II a HR about 1.55 across all age. More attenuated associations with higher age were found in individuals with the highest obesity using the fat mass index. Very high lean mass was associated with an increased risk of mortality in those aged 55 to 75 years (HR about 1.20 across all age).

Conclusion: Obesity should be prevented at any age. Attenuated associations with older age were observed only among the individuals with the highest obesity, but the risk

remained higher compared to normal weight participants. Lean mass did not reduce mortality risk at any age.

Keywords:

Body mass index; fat mass; fat-free mass; muscle mass; lean mass; ageing; survival; epidemiology

Introduction

Maintaining a healthy body composition is a cornerstone of chronic disease management and prevention. An excessive accumulation of body fat (i.e., adiposity) is associated with a higher risk of several chronic diseases such as cancer and cardiovascular disease incidence and mortality [1,2].

Many previous studies have used the body mass index (BMI) as a marker of adiposity when investigating the association between adiposity, chronic diseases, and mortality. However, the optimal BMI for reducing the risk of morbidity and premature mortality remains, to date, equivocal [3,4]. While some studies suggest that the BMI with the lowest mortality rate is within the normal weight range (18.5-24.9 kg/m2) [3,5], others have reported lower risk of mortality in the overweight range (25-30kg/m2) [6]. There is currently no distinction in BMI recommendations between younger and older adults. However, it is not implausible that the association between adiposity and risk of mortality varies across the lifespan. For example, it has been suggested that adiposity may provide larger metabolic reserves against frailty and diseases in older populations [7] Others have suggested that being overweight or even obese could be protective in older ages [8,9]. Previous epidemiological studies have reported attenuated associations between higher BMI and mortality in older adults compared to younger

individuals [3,5,10–12]. However, attenuated associations may also have methodological explanations including greater misclassification of adiposity with BMI in older individuals, or selection/collider stratification bias [13,14].

BMI can be a poor marker of adiposity, as it does not distinguish between fat mass and lean mass, which may have different associations with health outcomes. In addition, body composition changes with age, which may also explain age-specific associations of adiposity with mortality. Despite the benefits of lean mass on maintenance of independent functional capacity [15], studies have not consistently reported a clear association between lean mass and longevity [16,17], although some suggest a greater importance of lean mass over BMI for health outcomes at older ages [14].

Determining how total body mass, fat mass and lean mass are associated with mortality as a function of age may thus provide new insights into the role body composition plays in longevity. Capitalizing on a large sample of adults from the UK Biobank cohort, we aimed to ascertain the age-specific risks of mortality associated with different measures of body composition.

Methods

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [18] (checklist available in Supplementary Table 1).

Data source and study population

This prospective study is based on data from the UK Biobank (Application Number 29717). The UK biobank is a population-based cohort of 502 682 participants aged 37 to 82 years recruited between 2006 and 2010 across 22 assessment centers in England, Wales, and Scotland. Upon providing written consent, data collection included a touch-screen questionnaire, a wide number of physical measurements, biological sampling, and linkage to

electronic registries. Ethical approval was obtained by the North-West Research Ethics Committee. Details of the protocol are available elsewhere [19].

Measures

Obesity and body composition

Obesity was based on BMI and body composition from fat mass index (fat mass(kg)/height(m)^2) and lean mass index (lean mass(kg)/height(m)^2). As supplementary adiposity indices, we included waist circumference (a surrogate marker of central adiposity) and body fat percentage.

BMI was calculated from measurements during the initial visit at the assessment center as weight(kg)/height(m)^2. We categorized participants into underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), obesity class 1 (BMI 30.0-34.9 kg/m^2) and obesity class 2 (BMI ≥35 kg/m^2) [20]. Body composition measures were derived from bio-impedance measurements using a Tanita BC-418MA body composition analyzer (Tanita Corporation, Tokyo, Japan). Since there are no established population-based cut-points for fat or lean mass, we created four categories based on the sample distribution by mirroring the sex-specific distribution of the BMI categories as follows: low, medium-low, medium-high, and high fat mass index, lean mass index and body fat percentage [21]. For example, the distribution of the sample in fat mass index categories was identical to established BMI categories (e.g., 42% women with normal weight BMI would yield 42% women with low fat mass index, although not necessarily contain the same individuals). As waist circumference is highly correlated with BMI [22], we created a central-adiposity index that was independent of total adiposity by regressing waist circumference on BMI and categorizing the residuals using the same distribution-based approach as for fat mass index, lean mass index and body fat percentage. All anthropometric measurements were performed by trained clinical staff following standardized protocols [19].

Mortality

Death certificates held by the National Health Service (NHS) Information Centre for participants (England and Wales) and the NHS Central Register Scotland (Scotland) were used to obtain date of death. We calculated person-years from participant's contributed follow-up to the date of death, emigration, loss to follow-up or 31 March 2020, whichever came first.

Covariates

We calculated age as the difference between date of birth and date of baseline assessment. Self-reported sociodemographic covariates included ethnicity (White, Asian, Black, others, mixed race), education (no qualifications, qualifications different from college or university degree, and college or university degree), marital status (living with partner, not living with partner) and employment status (employed, not employed). The Townsend deprivation index was used as a marker for area-based socioeconomic status, derived from postcode of residence and census data on housing, employment, social class, and car availability [23].

Physical activity was calculated as metabolic equivalents (METs)-minutes/week following standardized protocols, using an adapted version of the International Physical Activity Questionnaire Short Form [24]. We created an index reflecting dietary pattern based on meeting two out of three healthy eating targets: 1) ≤3 weekly servings of red meat and ≤1 servings/week of processed meat; 2) ≥2 servings/week of fish including at least one with oily fish; 3) ≥5 servings/day of fruits and vegetables [25]. We also adjusted our models for the frequency of adding salt after cooking (never, sometimes, usually, and always), alcohol intake (never, previous, current and <3 times/week, current and ≥3 times/week) and smoking status (never, previous, and current). In addition, models were adjusted for leisure-time screen use, estimated as time spent watching TV and using a computer outside of work (<2, 2-3, 3-4, 4-5, and >5 hours/day). History of depression (yes, no; extracted from verbal interview with a trained nurse) was also considered.

A total of 250 480 participants had complete data on exposures, outcome, and covariates. By performing multiple imputation using chained equations with 10 data sets generated, we could retrieve missing data on covariates for an additional 119 272 participants (Supplementary Figure 1). The model for multiple imputation included all exposures, the cumulative hazard function, and covariates, along with additional health-related variables to increase precision (household income, systolic and diastolic blood pressure, presence of diabetes, and self-reported weight change in the previous year to baseline measurements, walking pace, use of beta-blockers, calcium channel-blockers or statins, asthma, and general health perception). Additional detailed information regarding variable extraction and coding is presented in Supplementary Table 2.

Statistical Analyses

We examined how the association between BMI and body composition categories with all-cause mortality varies as a function of age, from 45 to 85 years, using flexible parametric survival hazard models (Royston-Parmar models, stpm2 package for Stata 17 [StataCorp LP, College Station, TX, USA]), with age as the underlying timescale and restricted cubic splines with two degrees of freedom [26]. Increasing the degrees of freedom did not show differences in the hazard ratio (HR) curve for most models, while it created convergence problems and suggested overfitting in some models (about 40% of those in the sensitivity analyses). Models were adjusted for the covariates described above. Models using fat mass index as the exposure were further adjusted for lean mass index and vice versa [27]. We presented the results of our models in plots, interpreted as the HR for all-cause mortality at the specific age-point on the x-axis (e.g., the HR at age 70 is interpreted as the HR for death at age 70).

To reduce the potential bias from reverse causality (i.e., underlying known or unknown health conditions leading to weight loss), we started follow-up in all models five years after baseline and excluded participants with a wide variety of health conditions at baseline,

including chronic diseases (e.g., prevalent cancer and cardiovascular, neurodegenerative, immunological, or systemic diseases), underweight or mobility limitations [3,5] (information detailed in Supplementary Figure 1).

Based on previous studies [3,4], we repeated the analyses stratified by sex. We also conducted analyses restricted to participants who had never smoked [3,5], and to those who reported being weight stable the year prior to the baseline measurements. For these analyses, the age range was restricted to 50 to 85 years of age, due to the low number of events in the youngest (i.e., <50 years) age range.

All statistical analyses were performed using Stata 17 software (StataCorp LP, College Station, TX, USA).

Code availability

The code used for data curation and analysis is summarized in Supplementary table 2 and the full code is available upon request to the corresponding author.

Results

A total of 369 752 participants were included in the analysis (mean ± standard deviation baseline age = 56.3 ± 8.1 years; range 38.9 to 73.7 years; 54.1% women). The median follow-up was 11.4 years (4 104 740 person-years at risk). After truncating the first 5 years of follow-up, 4 240 deaths were excluded, a total of 10 660 deaths were recorded. The distribution of age at death is displayed in Supplementary Figure 2. Table 1 shows the baseline characteristics of the participants with complete records across BMI strata (the characteristics across fat mass index, lean mass index, waist circumference and body fat percentage strata are shown in supplementary tables 3, 4, 5 and 6, respectively). Bivariate Pearson's correlation coefficient (ρ) between exposures ranged between 0.63 and 0.97 and were similar across age strata (Supplementary Table 7).

[Insert Table 1 around here]

The risk of death increased with higher levels of BMI and fat mass index. Only participants in the highest category of lean mass had a higher mortality rate than the low lean mass reference (Figure 1). The association (HR) between BMI and mortality was weaker before 55 years of age and remained stable afterwards. In contrast, the association between fat mass index and mortality was somewhat attenuated with increasing age especially in the highest fat mass categories. The association between lean mass and mortality was stable across the included age-range. In more detail, based on BMI, being overweight was associated with a lower rate of mortality compared with normal weight in the 45-55 years age-group but had a generally similar mortality risk as those with normal weight. Participants with obesity class I showed a higher rate of mortality across the full age range with a peak HR of 1.20 (95% confidence interval [CI]: 1.08, 1.33) about age 60 which decreased to 1.14 (95%CI: 0.98, 1.30) at age 80. Similarly, obesity class II showed a consistent 55% higher rate of mortality irrespective of age. The association between the fat mass index and mortality declined from a HR of 1.19 (95%CI: 1.02, 1.36) at age 55 to 1.10 (1.02, 1.18) at age 75 and to 1.08 (0.96, 1.19) at age 80 in the second-highest category of fat mass index and from 1.68 (95%CI: 1.00, 2.35) at age 45, to 1.50 (1.32, 1.68) at age 65 and 1.32 (1.11, 1.52) at age 80 in those in the highest fat mass index category.

Results for waist circumference and body fat percentage (Supplementary Figure 3) followed the same pattern as the fat mass index: higher mortality risk in the two highest categories and a reduction in the HR with increasing age.

[Insert Figure 1 around here]

The sex-stratified analysis showed slightly different patterns of associations across age between men and women (Supplementary Figure 4). The magnitude of the differences varied across the body composition indices and were the most pronounced for BMI. The association

between BMI and mortality was generally stronger in younger women compared with younger men, but weaker in older women compared with older men. In contrast, associations using fat mass index were similar for men and women, especially in the highest category of fat mass index.

In the analysis restricted to never smokers (n=212 071; 4 588 deaths), the associations between adiposity indices and risk of mortality were more pronounced in the younger participants, especially when comparing those with obesity class II with the referent (Figure 2). A clear age-gradient was observed in the highest categories of all metrics with stronger associations observed in the youngest participants and diminishing magnitude of associations with increasing age (HRs 2.16 [95%CI 1.50, 2.82] at age 50 using BMI and 1.95 [95%CI: 1.31, 2.58] using fat mass index, and 1.42 [95%CI: 1.08, 1.74] for BMI and 1.12 [95%CI: 0.84, 1.39] for fat mass index at age 80, respectively). The results of waist circumference and body fat percentage among never-smokers are shown in Supplementary Figure 5.

[Insert Figure 2 around here]

The results from the sensitivity analysis restricted to people who reported no weight changes in the previous year to the baseline measurements are presented in Supplementary Figure 6. Results support the findings based on the full sample, showing no weakening of the association between BMI and mortality with older age. We observed weakening of the association between high fat mass index and mortality with increasing age, however, the magnitude of weakening was less pronounced compared with the analysis based on the full sample.

Discussion

We analyzed whether the associations between adiposity and mortality change from middle to old age. Our findings have important public health implications because they suggest that obesity should be prevented across the lifespan, including in individuals up to 85 years of age.

Being overweight was not associated with an increased risk of death regardless of the adiposity measures. In fact, we observed lower risk of mortality in older participants with overweight compared with normal weight when adiposity was assessed by the fat mass index. However, the magnitude of association was small and may not be clinically meaningful. A higher risk of mortality was observed participants with obesity (class I and class II) with similar magnitudes of association whether adiposity was measured by BMI or fat mass index. We did not observe attenuation of the associations between higher levels of BMI and mortality risk with age. Our results contradict previous studies reporting attenuated BMI-mortality associations when analyses were restricted to older individuals [3,5,10–12]. We did observe attenuated associations with higher age in individuals with the highest obesity when adiposity was measured by fat mas index, in line with previous studies using fat mass measurements [27]. However, mortality rates remained higher than in same-aged participants with low fat mass levels. Our results therefore question the idea that moderate levels of fat mass could be protective, which has been based on the hypothesis that higher body fat could provide larger metabolic reserves against frailty and diseases in older populations [7].

Associations between BMI and mortality were similar to those between fat mass index and mortality in magnitude and shape. We used fat mass index to express adiposity because it is a measure of body fat that is independent of body size [27]. Yet, age- and sex-specific correlations between fat mass index and BMI in this sample were ≥0.93, so the similarities between the associations involving the two measures of adiposity are therefore not surprising. Therefore, while only fat mass index was able to detect attenuated adiposity-mortality associations with advancing age in participants with the highest obesity, the clinical importance of the difference in effect size between BMI and fat mass index is not clear. Results from our data thus confirmed the utility of using BMI as a useful surrogate of adiposity in epidemiological studies in adults aged 45 to 85 years. Similarities between BMI and fat mass

index remained when we restricted our analysis to never-smokers. However, effect sizes for obesity increased in magnitude at younger age and the attenuation of effect sizes with advancing age was more pronounced, with HRs approaching 1 for fat mass index-determined obesity classes I and II at age 85. Restricting the analysis to never-smokers removes residual confounding from smoking, which was an issue raised by previous studies [3]. This often results in a left-shift of the BMI-mortality association where, compared with normal weight, increased mortality rates were observed at a lower BMI and often in the overweight range [3,5] observed in our data. This may be due to the lack of comparability between the overall sample and the subsample of never smokers.

While a larger metabolic reserve against frailty and diseases in older populations is a possible biological explanation for the attenuated associations between adiposity and mortality in old age, another potential explanation is methodological, namely the built-in selection bias of hazard ratios [28]. As hazard ratios compare participants 'at-risk', depletion of susceptible (frail) participants at younger ages mean that those reaching old age are a selectively healthier subgroup, which could be metabolically healthy while having obesity [12,29]. The aging process itself increases the risk of cancer, cardiovascular diseases, and frailty, making body composition a relatively less important risk factor for short-term survival [30]. Importantly, because we directly modelled the statistical interactions between age and body composition on mortality, our analysis is not directly comparable with previous studies which are based on analyses stratified by baseline age [3,5,6]. Whereas the stratified analysis estimates the mortality risk in participants with a particular baseline age (e.g., the hazard ratio of normal weight versus obesity among participants aged 70-80 years at baseline, followed for 10 years), the flexible parametric model we used is interpreted as the HR at a given age (e.g., normal weight versus obesity at age 70).

Higher lean mass did not show protective effects, even at older ages. Additionally, the group with the highest lean mass showed a 20% to 30% higher risk of mortality from about 55 to 75 years, a comparable (although attenuated) pattern of observations to the highest groups of the body and fat mass indices. While some studies reported null or inverse associations of lean mass with mortality, others found that higher lean mass has also been linked to higher mortality and worse health outcomes [16,17]. Previous authors have suggested that muscle quality matters more than quantity when it comes to cardiometabolic health, and future research should consider factors such as microvasculature, muscle fiber type distribution and size, fat infiltration, and fat-free mass function [17,31].

Strengths and limitations

Our study has several strengths. To address previous limitations, we directly modelled the associations as a function of age. We also followed recommendations to reduce reverse causation bias by excluding participants with a range of health conditions, starting the follow-up after the first 5 years, and performing a sensitivity analysis restricting to never smokers [3]. Furthermore, we included different measures of body composition, which were all assessed by professional staff, reducing the risk of systematic bias from self-reported anthropometric measurements [32]. Finally, we mutually adjusted for lean and fat mass index in respective models, which helps us tease out independent associations.

However, this study also has some limitations and findings should be interpreted with caution. First, low statistical power in the youngest participants may have provided unstable estimates in this age group. Second, we estimated the effect of adiposity at follow-up age using only one measurement of adiposity at baseline, under the assumption of no change in weight over time. To limit the influence of recent changes in body weight, we performed a sensitivity analysis in people who reported being weight stable during the last year. However, this timeframe may not be sufficient to fully capture the influence of unintended weight loss from

e.g., subclinical disease. Similarly, we did not have historical data on body composition before baseline and could not examine whether different years of exposure to obesity at different ages could influence the association with mortality. Future studies should include repeated measurements of body composition before and during follow-up to capture changes across time. Third, we derived body composition from bio-impedance, which is affected by the height, cross-sectional area, and ionic composition of the body [33]. Additionally, our strategies to reduce reverse causation bias may not be sufficient and limits generalizability to individuals with chronic conditions or short remaining life-expectancy [4]. Among participants with obesity, the differences in effect sizes between the main analysis and the sensitivity analysis in never-smokers may suggest that the main analysis is not free from smoking-related confounding. A caveat of restricting to never-smokers is limited generalizability of the data. Furthermore, our analysis could still be subject to survival bias and residual confounding due to unmeasured confounders and measurement biases of some covariates (e.g., diet). In addition, we included participants up to 85 years of age, so the shape and magnitude of associations at older ages warrants further investigation. Similarly, we were not able to analyze the associations in more extreme obesity groups (e.g., BMI > 40 kg/m^2), due to lack of statistical power. Finally, associations between risk factors and outcomes in the UK Biobank may not be generalizable [34] as there is evidence of a healthy volunteer selection bias [35].

In conclusion, obesity should be prevented at any age. Obesity, but not overweight, was associated with a higher risk of death from middle to older age irrespective of the adiposity index used. Attenuated associations with older age were observed only among the individuals with the highest obesity. Having a higher lean mass did not reduce mortality risk at any age.

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Author contributions

MASL, DD, KED, UE, and JT conceptualised and designed the study. MASL verified and analysed the data with help from JT, KED and BDPC. MASL takes responsibility for integrity of the data and the data analysis. MASL and JT wrote the first draft of the report. All other authors assisted in developing the statistical models, reviewed results, provided guidance on methods, and critically reviewed the manuscript. All authors had full access to the data and accept responsibility to submit for publication.

Competing Interests statement

The authors have nothing to disclose.

Data Availability Statement

The datasets analysed in the present study are globally accessible to approved researchers in the UK Biobank repository, https://www.ukbiobank.ac.uk/

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Table 1. Baseline characteristics of the included participants (n=369 752) by strata of Body Mass Index.

Figure 1. Age-varying hazard ratios for all-cause mortality in categories of body mass index, fat mass index and lean mass index in the total sample (n=369 752). Results adjusted for age (as time-scale), sex, ethnicity, education, living/not living with partner, employment, diet pattern, salt consumption, screen time, smoking, alcohol consumption, depression, Townsend Index and weekly physical activity. The model for body fat percentage was also adjusted by the Lean Mass Index.

Figure 2. Age-varying hazard ratios for all-cause mortality in categories of body mass index, fat mass index and lean mass index in never-smokers (n=212 071). Results adjusted for age (as time-scale), sex, ethnicity, education, living/not living with partner, employment, diet pattern, salt consumption, screen time, alcohol consumption, depression, Townsend Index and weekly physical activity. The model for body fat percentage was also adjusted by the Lean Mass Index.