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Stratified probabilistic bias analysis for BMI-related exposure misclassification in postmenopausal women

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Abstract

Background—There is widespread concern about the use of body mass index (BMI) to define obesity status in postmenopausal women because it may not accurately represent an individual's true obesity status. The objective of the present study is to examine and adjust for exposure misclassification bias from using an indirect measure of obesity (BMI) compared with a direct measure of obesity (percent body fat).

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Conflict of Interest: None to declare.

Data are available from the Women's Health Initiative coordinating center as well as through the NHLBI BioLINCC program. Software code for replication is available in the supplemental digital content.

Methods—We used data from postmenopausal non-Hispanic black and non-Hispanic white women in the Women's Health Initiative (WHI; n=126,459). Within the WHI, a sample of 11,018 women were invited to participate in a sub-study involving dual-energy x-ray absorptiometry (DXA) scans. We examined indices of validity comparing BMI-defined obesity (≥30kg/m^2) with obesity defined by percent body fat. We then used probabilistic bias analysis models stratified by age and race to explore the effect of exposure misclassification on the obesity-mortality relationship.

Results—Validation analyses highlight that using a BMI cutpoint of 30 kg/m^2 to define obesity in postmenopausal women is associated with poor validity. There were notable differences in sensitivity by age and race. Results from the stratified bias analysis demonstrated that failing to adjust for exposure misclassification bias results in attenuated estimates of the obesity–mortality relationship. For example, in non-Hispanic white women age 50–59, the conventional risk difference was 0.017 (95% CI 0.01, 0.023) and the bias-adjusted risk difference was 0.035 (95% SI 0.028, 0.043).

Conclusions—These results demonstrate the importance of using quantitative bias analysis techniques to account for non-differential exposure misclassification of BMI-defined obesity.

Keywords

bias analysis; obesity; body mass index

Introduction

Body mass index (BMI) is the most frequently used metric to categorize individuals according to their body weight status.[1–3] Despite the widespread use of BMI to define obesity in clinical settings and epidemiologic research, the limitations of using it as a measure of obesity status are well documented.[4–6] One concern about the use of BMI is that it may not accurately represent an individual's true obesity status, resulting in exposure misclassification. In this manuscript, we aim to explore the potential for exposure misclassification bias from using BMI to define obesity status in studies of the obesity-mortality relationship in postmenopausal women.

BMI-related misclassification may be amplified in postmenopausal women because after menopause, it is common for women to experience changes in body composition, including increased total body fat and an accumulation of abdominal fat, as well as decreased muscle and bone mass and height loss.[6–10] Considering the known physical changes that occur as women age, it is unlikely that a BMI value of 30 kg/m^2 corresponds to the same amount of body fat in pre- and postmenopausal women. The extent to which BMI-related misclassification of obesity status influences the evaluation of hypotheses pertaining to obesity and health outcomes in postmenopausal women is unclear. Additionally, previous research has demonstrated that race is an important determinant of body composition and obesity.[11,12] The validity of BMI-defined obesity may differ across racial groups as the relationship between BMI and percent body fat, muscle mass, fat distribution and bone mineral density differ among black and white women.[11,12] White women who are obese are known to have greater body fat than obese black women at a given BMI value.[11]

Considering the known age-related and racial differences in body composition in postmenopausal women, in the present manuscript we stratified all analyses by age and race.

In this paper we describe differences in the validity of BMI-defined obesity status by age and race and quantify the impact of exposure misclassification bias resulting from using BMI-defined obesity as a proxy for true adiposity status in postmenopausal women. The manuscript includes results from two analyses: (1) a validation study exploring the sensitivity and specificity of obesity classification defined by BMI compared with percent body fat measured using dual energy x-ray absorptiometry (DXA) scan, and (2) a bias analysis to investigate the impact of BMI-related misclassification on the association between obesity and all-cause mortality in postmenopausal women.

Methods

Study Design and Participants

Between 1993 and 1998, the Women's Health Initiative (WHI) enrolled 161,808 postmenopausal women aged 50–79 at 40 clinical centers across the United States.[13–15] The WHI is a longitudinal study designed to examine causes of morbidity and mortality in postmenopausal women. It comprises an observational study and clinical trial and included comprehensive questionnaires on medical history, demographic information, and lifestyle behaviors as well as clinical visits, collection of biologic specimens, and in-person interviews.[16] To increase the generalizability of study results, the inclusion criteria for the WHI were broad.[16] Women were only excluded if they had a medical condition predictive of less than 3 years survival or a condition that interfered with adherence and participation (e.g., dementia), or if they were actively participating in another clinical trial.[16] The study protocol was reviewed by institutional review boards at each of the clinical centers as well as the WHI Coordinating Center.[17]

All women recruited to participate in the WHI at three of the clinical centers (Pittsburgh, Birmingham, and Tucson-Phoenix) consented to have DXA scans as part of their study visits at baseline and at years 3,6, and 9.[8] There was no additional consent form required for DXA participants; this procedure reduced the likelihood of differential participation in the sub-study. Participants from these three centers form the WHI DXA sub-cohort (Pittsburgh n=3590; Birmingham n=3665; Tucson-Phoenix n=3765). Of the women screened at each of the three DXA centers, 90% had a DXA scan. Reasons for ineligibility for DXA included predefined criteria, such as bilateral hip replacement (prosthesis). The age distribution of participants in the DXA sub-cohort is similar to the distribution in the larger WHI cohort. The DXA sites were chosen because they were expected to have a good representation of participants from diverse race/ethnicity groups.[18] Body composition, site-specific and whole-body bone density were measured through a whole body DXA scan using a Hologic QDR-4500A densitometer (Hologic Inc, Bedford MA). DXA scans were performed according to standard protocol by trained technicians.[19]

Data from the WHI DXA sub-cohort served as an internal validation study. All participants at the three selected clinical sites were invited to participate in the sub-cohort; inclusion was not dependent on any other characteristics and all women had BMI measures and DXA scan

completed at the same study visit.[8] Only women in the DXA sub-cohort were included in the analysis for the validation study (n=11,018). For the purpose of the bias analysis, data from all non-Hispanic white and non-Hispanic black women in the WHI at baseline was used (n=126,459). Women were excluded if they had a missing BMI value at baseline (n=1,076). Information about the breakdown of participants from each cohort can be found in eAppendix 1 as well as additional information on age- and race- specific participation rates in the DXA subcohort.

Measures

In the present analysis, obesity is defined as BMI ≥ 30kg/m^2.[20] The height and weight values used to calculate BMI were measured by trained technicians using a calibrated scale and fixed stadiometer. Body fat percentage was calculated as total body fat mass divided by total mass multiplied by 100.[21,22] Validation studies and review articles have indicated that body fat percent from DXA scan is an appropriate gold standard for the measurement of obesity; however, there is a lack of consensus about what threshold value should be used to define obesity.[19,23,24] Based on a review of the substantive literature on body composition in older women, in this analysis, women who had a body fat percent greater than 40% were considered obese.[24–27]

The outcome variable in the bias analysis was all-cause mortality. The present analysis includes mortality follow-up through September 2016. The WHI coordinating center collects information on vital status through mail and telephone contacts with participants or participants' relatives, medical record assessments, obtained death certificates, and the National Death Index.[7]

Information on covariates was ascertained from study questionnaires at baseline and throughout follow-up. We identified predictors of misclassification from a search of the substantive literature on obesity, body composition, and mortality, including cigarette smoking status (never/former/current), total recreational physical activity level (metabolic equivalent of task (MET) hrs/week), hormone therapy use (never/former/current) and number of years since menopause. For the bias analysis, we additionally controlled for confounding by education, income level, marital status, alcohol consumption, and employment status as these are all variables known to affect obesity status and mortality risk. All analyses were stratified by race (non-Hispanic white and non-Hispanic black) and baseline age (50–59, 60–69, and 70–79).

Statistical Analysis

Stata 14 (College Station, TX) was used for all analyses. Software code is provided in eAppendix 2.

Analysis 1: Validation Study

Using baseline data from the WHI DXA sub-cohort, we modeled sensitivity and specificity with logistic regression. Sensitivity is the proportion of individuals who are truly obese according to DXA measurement of body fat percent (≥ 40%) who are classified as obese according to BMI, while specificity is the proportion of individuals who are truly non-obese

(body fat < 40%) who are classified as non-obese according to BMI. An advantage of using this modeling approach to calculate sensitivity and specificity is that it allows for stratification by age and race as well as adjustment for predictors of misclassification. In this analysis, obesity defined by BMI is the outcome variable; an individual was assigned Y=1 if their BMI ≥ 30 kg/m^2 or Y=0 otherwise, and true obesity status is included as a binary exposure variable (i.e., X_1=1 if BF ≥ 40%; X_1=0 otherwise).[28] The log odds of the outcome is modeled as a linear function of the exposure variable (X_1) and a vector of covariates (Z):

$$logit \Pr(Y = 1 \mid X_1, Z)) = \beta_0 + \beta_1 X_1 + \beta_2 Z$$

The variables in Z were predictors of misclassification: smoking status, hormone therapy use, physical activity level, and number of years since menopause. The analysis was stratified by age and race, thus a separate model was fit for each strata of non-Hispanic white and non-Hispanic black women aged 50–59, 60–69, and 70–79.

Sensitivity is then calculated from the following formula:

$$Sensitivity = \frac{1}{1 + exp[-(\beta_0 + \beta_1 X_1 + \beta_2 Z)]}$$

And specificity is calculated as:

$$Specificity = 1 - \left\{ \frac{1}{1 + exp[-(\beta_0 + \beta_1 X_1 + \beta_2 Z)]} \right\}$$

When calculating sensitivity, X_1=1 and when calculating specificity, X_1=0. The delta method was used to estimate 95% confidence intervals for the sensitivity and specificity parameters. As a sensitivity analysis, we compared these results to sensitivity and specificity values calculated using data from repeated DXA study visits (baseline, years 3,6, and 9; see eAppendix 3).[28]

Analysis 2: Bias Analysis

We used the estimates from the validation study to conduct a stratified probabilistic bias analysis with Monte Carlo sampling techniques to adjust for non-differential exposure misclassification. The bias analysis was conducted within the previously described age and race strata.[29] Throughout this manuscript, we use ‘non-differential exposure misclassification’ to refer to a systematic error in classification of BMI-defined obesity status that is independent of exposure or outcome status.[5]

This method for bias analysis has been described in detail elsewhere.[30,31] The bias analysis consists of three parts: (1) modeling the bias parameters, (2) record-level correction for exposure misclassification, and (3) estimating effect of obesity on mortality using the bias-adjusted exposure variable.[32] We then compared the results of the bias-adjusted analysis with the results of a conventional statistical analysis.

Modeling Bias Parameters—The sensitivity and specificity values were used to calculate positive predictive values (PPV) and negative predictive values (NPV) for each age and race strata.[31] PPV represents the probability of correct classification, that is, the probability that a woman originally classified as obese by BMI was correctly classified. NPV is the probability that a woman originally classified as non-obese by BMI was correctly classified.

To incorporate binomial error in the sensitivity and specificity values, we used beta distributions to model the probability density functions.[30,32] The shape of the distribution is determined by two parameters: α and β. For both sensitivity and specificity, we started with the α and β values calculated from the observed data and adjusted the values (i.e., increasing α or β) as required so the mean of the beta distribution ($= \alpha/\alpha+\beta$) accurately reflected the predicted sensitivity and specificity values calculated from the multiple logistic regression model in the validation data. A separate beta distribution was used to model each of the stratum-specific sensitivity and specificity values.

Calculating PPV and NPV takes several steps using the observed data, sensitivity, and specificity values (see Figure 1):[31] 1) use the observed data to calculate the number of exposed (E+) and unexposed (E−) individuals at each level of the outcome (D− and D+) for each age-race strata (Figure 1a), (2) use the observed data, and the sensitivity and specificity values drawn from the beta distributions, to calculate the values for 2×2 table that you would expect to see had there been no misclassification (Figure 1b), (3) use the expected values, sensitivity, and specificity to calculate the number of expected true positives (TP), true negatives (TN), false positive (FP) and false negatives (FN) at each level of the outcome (Figure 1c), and (4) calculate the PPV and NPV values for each strata at each level of the outcome (Figure 1d). There were 12 PPV and 12 NPV values calculated for non-Hispanic black and non-Hispanic white women aged 50–59, 50–69, and 70–79 at each level of the outcome. Given the validation data available, it was possible, in theory, to calculate the PPV and NPV from the data directly, but the age and race stratified data from the validation study were very sparse when further stratified by outcome group (see eAppendix 4). The sparse outcome-level data was an obstacle to calculating PPV and NPV directly, as we wanted to ensure that we would be able to calculate predictive values with a reasonable level of precision to inform the bias analysis.[33] Considering this limitation, using the sensitivity and specificity to calculate the PPV and NPV is a valid technique to use in the present analysis.[31]

Record-level correction for exposure misclassification—The predictive values were then applied to each record (observation) in the dataset to simulate whether an individual was correctly classified.[31] All PPV and NPV values used in the record-level bias correction were age and race specific, meaning the probability of correct classification for a 50–59 year old non-Hispanic white woman may differ from the probability of correct classification for a 60–69 year old non-Hispanic black women.

Classified obesity was a dummy variable with 1 indicating obesity and 0 indicating non-obesity. To model whether an individual observation was correctly or incorrectly classified, for each subject in the dataset we conducted a Bernoulli trial with a probability equal to the

relevant PPV for those who were classified as obese and 1-NPV for those classified as not obese. The result of this trial was used as the bias-adjusted exposure.[31,34] Exposure status was left unchanged for women who were part of the DXA sub-cohort. Once this reclassification process is conducted for each record in the dataset, we have simulated a single new, bias-adjusted, dataset.

Estimating the obesity-mortality relationship—Using the bias-adjusted dataset, we then used a logistic regression model and marginal standardization to calculate the average marginal effects associated with obesity.[35,36] The average marginal effect is the change in the conditional mean of the outcome per unit change in the exposure, conditional on the covariates included in the model. The interpretation of the average marginal effect is similar to a risk difference. We used the -margins- command in Stata to estimate the marginal standardized risk in the exposed and unexposed participants and then take the difference of these means.[37,38] We additionally calculated hazard ratios from a discrete time hazards regression model so our results are readily comparable with the broader literature on obesity and mortality, as this is the most frequently used effect estimate. However, we acknowledge that the hazard ratio shares many of the limitations of the odds ratio.[39]

This entire process (i.e., sampling from the beta distributions for sensitivity and specificity, calculating PPV and NPV, reclassifying individual records in the dataset to generate a new dataset and then calculating stratified bias-adjusted risk difference) was repeated 80,000 times to create a distribution of risk differences. The bias-adjusted effect estimate reported is the 50^{th} percentile of the distribution for each age and race/ethnicity strata. The 2.5^{th} and 97.5^{th} percentiles of the distribution provide a 95% simulation interval around the bias adjusted estimate that only accounts for systematic error. In order to also account for total study error (i.e. systematic and random error), we subtracted the product of the conventional standard error and a random normal deviate from each of the bias-adjusted estimates. We repeated the same process of 80,000 iterations to calculate the bias-adjusted hazard ratios.

We compared the effect estimates from a conventional analysis, using obesity defined by measured BMI as the primary exposure and all-cause mortality as the outcome (“conventional results”) with the effect estimates from the bias analysis (“bias-adjusted results”).

Results

Participant Demographics

The analytic cohort included data from 126,459 women, 69,690 from the WHI observational study and 56,769 from the clinical trial. At baseline, the average age was 63 ± 7.1 years for non-Hispanic white women and 61 ± 6.9 years for non-Hispanic black women. The prevalence of BMI-defined obesity (BMI ≥30 kg/m^2) was 28% for non-Hispanic white women, and 50% for non-Hispanic black women. Using a 40% body fat cutpoint to determine obesity, 71% of non-Hispanic white and 81% of non-Hispanic black women were classified as obese. Table 1 contains additional demographic information on the DXA subcohort used in the validation study and total WHI cohort used in the bias analysis.

Table 2 presents a summary of baseline anthropometric characteristics stratified by race and age group. Interesting differences emerged when comparing body weight and body composition across groups. In general, there is a pattern of attenuation in these characteristics across age groups. Height, body weight, body fat, lean mass, and bone density all decrease as women age, regardless of race/ethnicity (see Figure 2). Across all age groups, non-Hispanic black women had markedly higher body weight, BMI, body fat, and lean mass values than non-Hispanic white women. The difference in mean weight comparing non-Hispanic black women to non-Hispanic white women is particularly striking. In the youngest age group, on average, non-Hispanic black women weighed 10 kg more than non-Hispanic white women.

Results of validation study comparing obesity defined by BMI vs body fat percent

Results comparing sensitivity and specificity of BMI-defined obesity with obesity defined by percent body fat are presented in Table 3. The sensitivity of BMI-defined obesity was higher in non-Hispanic black women than non-Hispanic white women. Estimates increased after accounting for smoking, hormone therapy use, physical activity level, and number of years since menopause, all variables known to influence body composition and body weight. There was a consistent pattern of declining sensitivity across age strata. In both black and white women, the sensitivity of BMI to define obesity was lower in the 70–79 year old group than the 50–59 year old group. The magnitude of the age-related difference in crude sensitivity values was consistent in both race groups (non-Hispanic white: 35.0–44.7= −9.7%, non-Hispanic black: 45.6–55.7=−10.1%). However, there was a greater discrepancy in the decline of the adjusted sensitivity values. In non-Hispanic white women, adjusted sensitivity values were 56.8% (95% CI: 52.9, 60.7) in 50–59 year olds, 49.5% (95% CI: 45.1, 53.8) in 60–69 year olds and 42.1% (95% CI: 36.2, 48.1) in 70–79 year olds. The adjusted sensitivity values in non-Hispanic black women were 73.7% (95% CI:65.5, 82.8) in 50- to 59-year olds, 59.7% (95% CI: 55.1, 64.3) in 60- to 69- year olds and 52.4% (45.9, 58.9) in 70- to 79-year olds.

Results of bias analysis investigating impact of BMI-related misclassification on the obesity-mortality relationship

Over the follow-up period, there were 21,459 deaths due to all causes (16%) in the total cohort. Of those deaths, 19,576 (91%) were among non-Hispanic white women and 1,362 (6%) among non-Hispanic black women.

The results of the bias analysis are presented in Table 4. After adjusting for both random and systematic error, the mortality risk difference is similar in white and black women aged 50–59 (see Table 4). The bias-adjusted mortality risk difference increased in both non-Hispanic white and non-Hispanic black women aged 60–69, to 651 per 10,000 (95% SI: 588, 713) in white women and 794 per 10,000 in black women (95% simulation interval [SI]: 352, 1284). However, in non-Hispanic white women aged 70–79, the mortality risk of obesity decreased to 466 per 10,000 women (95% SI: 278, 654), but a similar decline was not seen in non-Hispanic black women (779 per 10,000 women; 95% SI: 6, 1571). These results provide some evidence of effect modification by age and race. As expected, the 95% simulation

intervals (SI) for the bias-adjusted estimates are wider than the 95% confidence intervals for the conventional estimates across all age and race groups.

Table 4 also contains conventional and bias-adjusted hazard ratios for the effect of obesity on mortality. The results consistently demonstrate that BMI-related non-differential misclassification of obesity status produces a substantial bias toward the null, leading to an underestimate of obesity-related mortality risk in this sample of post-menopausal women. Comparison of the bias-adjusted and conventional results shows that the bias-adjusted estimates were greater than conventional estimates across all age categories in both black and white women.

Discussion

Using data from a large prospective cohort of postmenopausal women, our results highlight differences in the validity of BMI as a measure of true obesity status among postmenopausal non-Hispanic white and non-Hispanic black women. Accounting for misclassification of obesity status defined by BMI using probabilistic bias analysis yielded results that were greater than conventional estimates of obesity defined by BMI. Non-differential exposure misclassification of BMI-defined obesity resulted in attenuated estimates of the relationship between obesity and mortality.

Descriptive results from the current study provide additional insights into racial variation in body composition in post-menopausal women across different age groups. Race and ethnicity are known to be important determinants of body composition and obesity.[11,12,40] Non-Hispanic black women had the highest values for all of the components of body weight (i.e., fat mass, lean mass, and bone mass) as well as the highest average BMI values at ages 50 to 79, which is consistent with previous studies.[7,12,41] In a study of reproductive aged women (ages 16–33 years), Rahman et al., reported a similar pattern of findings: body fat, lean mass, and BMI were all higher in black women than white women.[11] Further research is required to examine the complex relationship between changes in the proportions of each of the components of body composition (i.e., fat mass, lean mass and bone density) and BMI in older women of different racial groups. At a fixed BMI level, there is great heterogeneity in body composition across women of different race and age groups.[12] Previous research has demonstrated that the proportion of women correctly classified as obese by BMI cutpoints decreases as women age.[24,25] These findings speak to the importance of stratifying on age and race when adjusting for BMI-related misclassification of obesity status. Our results highlight that not only does the relationship between BMI and body fat change as women age, the change is differs according to race.[24,26]

There has been debate in the scientific literature about whether there is a need for population subgroup-specific BMI-cutpoints to define obesity or whether BMI is the best measure to use to assess obesity altogether.[26,42,43] Asian-specific BMI cutpoints are now widely recognized, yet a BMI cutpoint of 30 kg/m^2 is used to define obesity in all other adult populations.[44] Age- and sex- specific BMI Z-scores are used to define obesity in children and adolescents to account for the fact that childhood is a time of rapid growth and physical change.[45,46] However, the same considerations are not made for older adults, despite our

knowledge of the physical changes that occur with aging. The present results demonstrate that there is potentially a need to consider different cutpoints to define obesity in older women or move away from using BMI cutpoints altogether. One interesting suggestion is that BMI may be a useful tool to define obesity at a population level (i.e., as a screening tool or to describe differences in populations) but should not be used to make individual level treatment decisions, owing to the fact that it does not account for location of adipose tissue (visceral vs. subcutaneous) nor body composition (muscle vs. lean vs. bone mass).[47] There is also much work to be done to understand the relationship between BMI-defined obesity and disease risk in older women.[48,49]

To the best of our knowledge, the present results are the first to use stratified probabilistic bias analysis to account for the effect of race and age on obesity-related exposure misclassification. Non-differential misclassification of a binary exposure typically leads to a bias toward the null, thus failing to account for this type of misclassification produces attenuated effect estimates.[29,50,51] This is consistent with our results, as we found that conventional estimates were nearer to the null than bias-adjusted estimates, although in some strata, there was overlap in the confidence intervals for bias-adjusted and conventional estimates. The logic behind this is straightforward: if non-differential exposure misclassification produces attenuated effect estimates, adjusting for this bias should result in increased effect estimates. An interesting avenue for future research is to investigate whether this form of exposure misclassification bias has produced a systematic underestimate of obesity-related mortality risks in older adults in the scientific literature.

Although the link between obesity and mortality has been well-established in young and middle-aged adults, there is less consensus about the effect of obesity on mortality in older adults.[1,52] In a meta-analysis examining the effect of obesity on mortality, Flegal and colleagues reported that obesity (BMI ≥30 kg/m^2) was not associated with mortality in adults over age 65 (HR=1.02; 95% CI=0.81–1.29). Other WHI investigators have also questioned the strength of the obesity–mortality relationship in postmenopausal women.[7,41] Research by Chen et al. demonstrated a decrease in the hazard ratio of mortality comparing obese (BMI 30–34.9 kg/m^2) to normal weight (BMI 18.5 to 24.9 kg/m^2) as women age but no evidence of effect measure modification by race (HR_{white}=1.02; 95% CI=0.97, 1.07 and HR_{black}=1.10; 95% CI=0.93, 1.31).[41] Previous work in the WHI has not explored the combined effect of age and race on the obesity–mortality relationship. The bias-adjusted risk differences we present herein do not show a consistent pattern of age-attenuation, but the hazard ratios do. This highlights an important point for investigators to consider when choosing between absolute and relative effect estimates.[53] One hypothesized explanation for the previously documented attenuation of obesity-related mortality in the literature is related to an increase in potential exposure misclassification bias when women age. As exposure misclassification increases, so too would the magnitude of the downward bias influencing effect estimates of the obesity–mortality relationship, producing an apparent attenuation of the effect. Another possible explanation for the different findings is the fact that our exposure was BMI ≥ 30kg/m^2, whereas Bea and Chen et al., explored the effect of 5-unit BMI categories on mortality (i.e. 25–29.9, 30–34.9, and ≥ 40 kg/m^2) compared with normal weight.

The threat of BMI-related exposure misclassification is a well-recognized concern in epidemiologic research. Exposure misclassification is frequently mentioned as a concern or limitation of published research, but few authors incorporate quantitative bias analysis tools into their work.[54] Probabilistic bias analysis is one empirical approach that can be used to adjust for misclassification. Our example included a misclassified exposure variable, but it could also be used to adjust for misclassification of confounding variables or outcome variables.[31] It is a flexible approach; since the bias adjustment occurs before any statistical modeling, the re-classified variables can then be used in any type of statistical analysis ranging from simple linear or logistic regression to survival analysis or complex analyses like inverse probability weighting or g-estimation.[31,32] A software macro has been developed to facilitate implementation of this bias analysis technique in SAS, and all Stata code from the present analysis is available in eAppendix 2. Other methods of quantitative bias analysis are also available but rely on adjusting sensitivity analyses of summary effect estimates.[55,56]

Our study has some limitations. For the purpose of conducting the bias analysis, we used BMI as a dichotomous variable. Dichotomizing a continuous variable is associated with a loss of information and specific assumptions (i.e., assuming individuals close to, but on opposite sides of the cutpoint are very different from each other).[57] We used DXA-defined body fat percent as the gold standard measure of adiposity. A strong body of literature demonstrates that body fat percent is an appropriate reference standard to use as a true measure of adiposity, but there is some debate about which cutoff point should be used to define obesity according to body fat percent.[4,24,25,40] Using body fat percent from a DXA scan as the gold standard does not incorporate information about the distribution of adipose tissue or numerous biologic complexities associated with different types of fat tissues which may impact estimates of the obesity-mortality relationship.[47] Also, since the women in the WHI cohort are all older and postmenopausal, our results are not generalizable to men or younger women, and it is possible that restriction to women who survived to cohort entry induced some selection bias.[58] Finally, we recognize that differences in the BMI–body fat percent relationship may exist for Hispanic women compared with non-Hispanic Black and non-Hispanic white women. As such, in eAppendix 5 we have included supplemental analyses in Hispanic women from the WHI exploring the validity of BMI and adjustment for BMI-related exposure misclassification.

Balancing these limitations, there are notable strengths of the present work. The large, well-characterized WHI cohort has excellent follow-up and is linked with the National Death Index. All anthropometric variables were measured using standardized techniques. The study investigators recruited women at three study sites to participate in the DXA subcohort, producing a valuable internal validation subsample. Our study makes a methodologic contribution to the epidemiologic literature by extending probabilistic bias analysis to include stratified bias analysis for exposure misclassification in settings when there is potential effect measure modification. The present results demonstrate the importance of incorporating probabilistic bias analysis in aging research, particularly researched focused on the effect of obesity in postmenopausal women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(a)

	E+	E-	Total
D+	a	b	a+b
D-	c	d	c+d
Total	a+c	b+d	n

(b)

	E+	E-	Total
D+	A= [a-(1-sensitivity) * N] / [sensitivity-(1-specificity)]	B= N-A	A+B
D-	C= [c-(1- sensitivity) * N] / [sensitivity -(1- specificity)]	D= N-C	C+D
Total	A+C	B+D	N

(c)

D+	D-
TP_{D+}= Sensitivity * A	TP_{D-} = Sensitivity * C
TN_{D+}= Specificity * B	TN_{D-} = Specificity * D
FP_{D+}= (1-sensitivity) * B	FP_{D-} = (1-sensitivity) * D
FN_{D+}= (1-specificity) * A	FN_{D-} = (1-specificity) * C

(d)

$PPV_{D+} = TP_{D+} / (TP_{D+} + FP_{D+})$

$NPV_{D+} = TN_{D+} / (TN_{D+} + FN_{D+})$

$PPV_{D-} = TP_{D-} / (TP_{D-} + FP_{D-})$

$NPV_{D-} = TN_{D-} / (TN_{D-} + FN_{D-})$

Figure 1.

Calculating positive predictive value and negative predictive value using observed data, sensitivity, and specificity. Note: E indicates exposure status (E+ for exposed, E− for unexposed) and D indicates outcome status (D+ for deceased, D− for non-deceased). TP = true positive; TN= true negative; FP= false positive; FN= false negative; PPV= positive predictive value; NPV=negative predictive value.

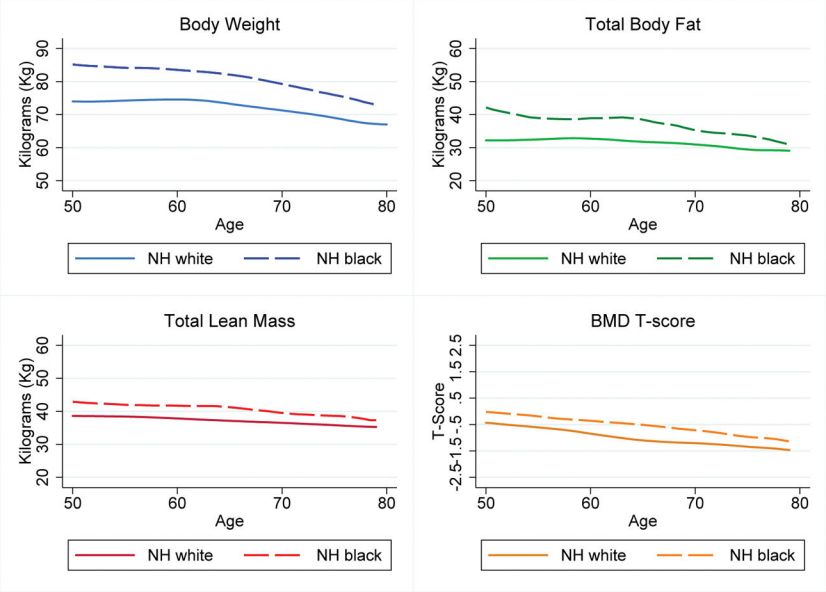

Figure 2.

Comparison of baseline body weight, total body fat, total lean mass, and bone mineral density (BMD) T-score and age among non-Hispanic (NH) white and non-Hispanic (NH) black women.

Table 1

Demographic characteristics comparing the Women's Health Initiative cohort (observational study and clinical trial) and WHI DXA sub-cohort at baseline

	WHI cohort (n=131,812)	WHI DXA sub-cohort (n=11,018)
Age (%)		
50–59 years	33	34
60–69 years	45	43
>70 years	22	23
Race/ethnicity		
Non-Hispanic Black	9	15
Non-Hispanic White	83	77
Hispanic	4	7
Other *	4	2
Education (%)		
Some high school	5	9
High school diploma or GED	17	23
Post-secondary	49	46
Post-graduate	29	22
Income		
<$50,000	62	74
$50,000–$75,000	20	15
>$75,000	19	11
Current smokers (%)	7	8
Current HRT users (%)	40	36
Married (%)	61	61
Moderate alcohol intake (1–7 drinks per week; %)	26	20
Employed (%)	37	32
Clinical trial participant, %	42	42
Recreational physical activity (total MET hours per week, mean ± SD)	12 ± 14	11 ± 14
Age at menopause, mean ± SD	48 ± 6	48

Note:

* Other race/ethnicity consisted of individuals who self-reported American Indian or Alaska Native, Asian or Pacific Islander, or Other

Table 2

Differences in baseline anthropometric characteristics of the Women's Health Initiative cohort stratified by age and race

	Non-Hispanic White			Non-Hispanic Black		
	50–59	**60–69**	**70–79**	**50–59**	**60–69**	**70–79**
Mean Height, cm	163.7 (6.4)	162.2 (6.3)	160.1 (6.2)	163.4 (6.4)	162.3 (6.6)	160.2 (6.5)
Mean Weight, kg	74.3 (17.1)	73.5 (16.0)	69.7 (14.3)	84.5 (19.6)	82.4 (17.9)	76.5 (17.2)
Mean BMI, kg/m^2	27.6 (6.0)	27.8 (5.7)	27.1 (5.1)	31.5 (7.0)	31.1 (6.4)	29.4 (5.7)
Total body fat, kg$^{\neq}$	32.5 (11.5)	32.0 (10.8)	29.9 (9.7)	39.8 (13.8)	38.4 (12.1)	33.8 (10.5)
Lean body mass, kg$^{\neq}$	38.5 (5.2)	37.2 (4.8)	35.9 (4.5)	42.2 (6.4)	41.2 (5.7)	38.7 (5.5)
Bone mineral density, t-score$^{\neq}$	−0.58 (0.95)	−1.07 (1.0)	−1.31 (1.1)	−0.15 (1.0)	−0.49 (1.08)	−0.98 (1.1)
Waist circumference, cm	84.9 (14.1)	86.5 (13.8)	85.6 (12.4)	91.8 (14.8)	91.8 (13.4)	89.1 (12.6)

Note:

$^{\neq}$indicates only participants from the DXA sub-cohort included (N=11,018). There were 115,722 white women in the total WHI cohort; n=37,346 aged 50–59, n=53,526 aged 60–69, and n=24,850 aged 70–79. There were 10,737 black women in the total WHI cohort at baseline; n=4632 aged 50–59, n=4644 aged 60–69, and n=1505 aged 70–79.

Table 3

Sensitivity and specificity (95% CI) of obesity defined by BMI (>30 kg/m^2) versus obesity defined by body fat percent (>40%) for non-Hispanic white and non-Hispanic black women stratified by age

	Non-Hispanic White			Non-Hispanic Black		
	50–59	**60–69**	**70–79**	**50–59**	**60–69**	**70–79**
Crude						
Sensitivity (%)	44.7 (42.6, 46.8)	39.8 (38.4, 41.1)	35.0 (32.8, 37.3)	55.7 (53.0, 58.3)	50.6 (48.3, 53.0)	45.6 (42.3, 48.8)
Specificity (%)	98.4 (97.8, 98.9)	98.7 (98.2, 99.1)	98.9 (98.5, 99.3)	97.5 (96.7, 98.3)	98.0 (97.2, 98.6)	98.3 (87.8, 98.9)
Adjusted						
Sensitivity[a] (%)	56.8 (52.9, 60.7)	49.5 (45.1, 53.8)	42.1 (36.2, 48.1)	73.7 (65.5, 82.8)	59.7 (55.1, 64.3)	52.4 (45.9, 58.9)
Specificity[a] (%)	96.8 (95.6, 98.0)	97.5 (96.7, 98.4)	98.2 (97.5, 98.9)	94.2 (91.9, 96.6)	96.4 (95.0, 97.8)	97.3 (96.2, 98.4)

[a]Adjusted for predictors of misclassification (smoking status, hormone therapy use, physical activity level, and number of years since menopause).

Table 4

Risk difference (RD) per 10,000 and hazard ratios (HR) for the effect of obesity on all-cause mortality comparing conventional analysis using measured BMI (conventional estimate) and bias analysis adjusting for misclassification (bias-adjusted estimate).

	Non-Hispanic White		Non-Hispanic Black	
	Conventional estimate[a] (95% CI)	**Bias-adjusted Estimate[a,b] (95% SI)**	**Conventional estimate[a] (95% CI)**	**Bias-Adjusted Estimate[a,b] (95% SI)**
RD per 10,000				
50–59	170 (100, 230)	353 (275, 431)	150 (−20, 330)	340 (98, 591)
60–69	270 (190, 340)	651 (588, 713)	60 (−17, 290)	794 (352, 1284)
70–79	290 (140, 440)	466 (278, 654)	27 (−25, 800)	779 (6, 1571)
Hazard ratio				
50–59	1.34 (1.22, 1.46)	1.82 (1.63, 2.01)	1.22 (1.05, 1.40)	1.67 (1.26, 2.23)
60–69	1.22 (1.11, 1.32)	1.63 (1.50, 1.76)	1.05 (0.91, 1.22)	1.94 (1.39, 2.81)
70–79	1.13 (1.07, 1.21)	1.24 (1.15, 1.33)	1.15 (0.87, 1.52)	1.54 (1.01, 2.22)

Note:

[a] Models were adjusted for smoking status, physical activity, hormone therapy use, years since menopause, education, income, marital status, alcohol consumption, and employment. SI =simulation interval, CI = confidence interval.

[b] Adjusted for systematic and random error (total error).