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## Use of self-reported height and weight biases the body mass index-mortality association

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### Abstract

**Background**—Many large-scale epidemiologic data sources used to evaluate the body mass index (BMI: kg/m<sup>2</sup>) mortality association have relied on BMI derived from self-reported height and weight. Although measured BMI (BMI<sub>M</sub>) and self-reported BMI (BMI<sub>SR</sub>) correlate highly, self-reports are systematically biased.

**Objective**—To rigorously examine how self-reporting bias influences the association between BMI and mortality rate.

**Subjects**—Samples representing the US non-institutionalized civilian population.

**Design and Methods**—National Health and Nutrition Examination Survey data (NHANES II: 1976-80; NHANES III: 1988-94) contain BMI<sub>M</sub> and BMI<sub>SR</sub>. We applied Cox regression to estimate mortality hazard ratios (HRs) for BMI<sub>M</sub> and BMI<sub>SR</sub> categories, respectively, and compared results. We similarly analyzed subgroups of ostensibly healthy never-smokers.

**Results**—Misclassification by BMI<sub>SR</sub> among the underweight and obesity ranged from 30–40% despite high correlations between BMI<sub>M</sub> and BMI<sub>SR</sub> ( $r > 0.9$ ). The reporting bias was moderately

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SWK is the guarantor of the paper, having had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. He had final responsibility for the decision to submit for publication.

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correlated with BMI<sub>M</sub> ( $r > 0.35$ ), but not BMI<sub>SR</sub> ( $r < 0.15$ ). Analyses using BMI<sub>SR</sub> failed to detect six of eight significant mortality HRs detected by BMI<sub>M</sub>. Significantly biased HRs were detected in the NHANES II full dataset ( $\chi^2 = 12.49$ ;  $p = 0.01$ ) and healthy subgroup ( $\chi^2 = 9.93$ ;  $p = 0.04$ ), but not in the NHANES III full dataset ( $\chi^2 = 5.63$ ;  $p = 0.23$ ) or healthy subgroup ( $\chi^2 = 1.52$ ;  $p = 0.82$ ).

**Conclusions**—BMI<sub>SR</sub> should not be treated as interchangeable with BMI<sub>M</sub> in BMI-mortality analyses. Bias and inconsistency introduced by using BMI<sub>SR</sub> in place of BMI<sub>M</sub> in BMI-mortality estimation and hypothesis tests may account for important discrepancies in published findings.

## Keywords

self-reported BMI; measured BMI; self-reporting bias; obesity; mortality; NHANES

## Introduction

Body mass index (BMI: kg/m<sup>2</sup>) has been used to show that excess body weight is highly prevalent<sup>1</sup>; associated with adverse medical conditions such as cardiovascular disease<sup>2</sup>, diabetes<sup>3</sup>, and many cancers<sup>4</sup>; and imposes personal and public health burdens in healthcare costs<sup>5</sup>, years of life lost<sup>6</sup>, and elevated mortality rate (MR)<sup>7-15</sup>. Many large-scale epidemiologic data sources (e.g., Nurses' Health Study<sup>14</sup>, the American Cancer Society Cancer Prevention Studies<sup>10</sup>, Health Professionals' Follow-up Study<sup>9</sup>, National Institutes of Health AARP<sup>7</sup>, and the Physicians' Health Study<sup>13</sup>) used to derive these findings do not contain measured heights and weights, but rely on self-reported height and weight. Although the results of studies using BMI<sub>SR</sub> and BMI<sub>M</sub>, such as the National Health and Nutrition Examination Survey (NHANES)<sup>11</sup> and the Prospective Studies Collaboration<sup>15</sup> typically show a U- or J-shaped relationship with MR in United States and International populations, respectively, disparities exist between results of some studies. Some BMI<sub>SR</sub> studies suggest that if ever-smokers and those with a history of disease or who died a few years after the baseline survey are excluded from the analysis, the relationship with MR among subgroups of ostensibly healthy never-smoker study participants is roughly monotonically increasing (e.g.,<sup>13-14</sup>). However, this result has generally not been observed in studies with BMI<sub>M</sub> (e.g.,<sup>15-16</sup>). To what extent might these differences result from using BMI<sub>SR</sub> in place of BMI<sub>M</sub>?

Although many studies have demonstrated that BMI<sub>SR</sub> provides a biased assessment of BMI<sub>M</sub><sup>17,32</sup>, BMI<sub>SR</sub> and BMI<sub>M</sub> still tend to be highly correlated ( $r > .90$ )<sup>21-24, 30-32</sup>. This led Manson et al. to write, "A validation study in the NHS [Nurses' Health Study], however, found a correlation of 0.96 between self-reported and measured weights, with the former averaging only 1.5 kg lower than the latter, and similar reporting accuracy was observed in NHANES III [the Third National Health and Nutrition Examination Survey], suggesting that self-reported weights may not introduce significant bias<sup>33</sup>." Alternatively, referring to the health and smoking subgroup analyses frequently conducted to explain apparently discrepant results, Flegal et al. wrote, "Depending on the characteristics of the subgroup, confounding by other variables might even be increased after such exclusions. In studies with self-reported weights and heights, differences in reporting error patterns between the full sample and the subgroup could also potentially affect the results<sup>16</sup>."

We investigate if using BMI<sub>SR</sub> in place of BMI<sub>M</sub> biased mortality results in nationally-representative datasets having both BMI<sub>M</sub> and BMI<sub>SR</sub>. We begin with a brief prefatory analysis of the relationship between these measures. This is followed by a summary of MR parameter significance tests as well as direct tests for bias in BMI<sub>SR</sub> MR estimates. We also repeat the tests in subgroups of ostensibly healthy never-smoker participants to evaluate Flegal et al.'s conjecture<sup>16</sup>. This is not merely a theoretical exercise because epidemiologic studies which relied on BMI<sub>SR</sub> have influenced public health opinions, recommendations, and policies. Hence, evaluating the validity of BMI<sub>SR</sub> as a substitute for BMI<sub>M</sub> is important.

## Materials and Methods

### Overview of datasets

The data come from two waves of NHANES. NHANES II was conducted from 1976 to 1980 on a nationwide probability sample of individuals aged 1 to 74 years. Mortality information was available for participants 30 years of age or older from the NHANES II Linked Mortality File. NHANES III was conducted from 1988 to 1994 on a nationwide probability sample of individuals aged 1 to 90 years. Mortality information was available for subjects 18 years of age or older from the NHANES III Public-Use Linked Mortality File. We limited our analyses to those aged at least 25 years at survey.

NHANES II and III design and sampling methods have been reported<sup>34-35</sup>. Mortality follow-up was drawn from the National Death Index. The NHANES III mortality follow-up times we analyzed in the public-access data were perturbed for decedent records by NCHS to protect confidentiality. A comparative study on the perturbed and unperturbed data suggest that using the perturbed data will not likely affect the results of survival analyses<sup>36</sup>. Pregnant participants or those with missing data on our study variables were given zero weight in analyses. As we were interested in how BMI<sub>SR</sub> might perform in population studies of BMI and mortality, we did not exclude participants having otherwise complete study data, but who were missing either BMI<sub>M</sub> ( $n_{\text{NHANES II}} = 0$ ,  $n_{\text{NHANES III}} = 3$ ) or BMI<sub>SR</sub> ( $n_{\text{NHANES II}} = 191$ ,  $n_{\text{NHANES III}} = 914$ ).

### Study variables

**Predictor**—Both measured and self-reported height and weight were available to calculate BMI<sub>M</sub> and BMI<sub>SR</sub>, respectively. Categories for BMI<sub>M</sub> and BMI<sub>SR</sub> were constructed according to federal guidelines<sup>37</sup> for defining underweight (<18.5), normal weight (18.5 to <25), overweight (25 to <30), obese (30 to <35), and severely obese (>35).

**Outcome variables**—Mortality status (i.e., alive or dead) and age at time of death or censoring<sup>38-39</sup> with follow-up through 1992 for NHANES II and 2000 for NHANES III.

**Covariates**—Data on gender, race (black, white, or other), alcohol consumption (average daily for NHANES III: 0, <0.07, 0.07 to <0.35, 0.35 oz/d; frequency for NHANES II: never, < 1 time/week, 1 to < 3 times/week, > 3 times/week), and smoking status (never, former, current).

## Statistical analysis

We have conducted our analyses in two stages. First, a brief prefatory analysis of the relationship between BMI<sub>M</sub> and BMI<sub>SR</sub> was conducted. Sample weighted misclassification rates were tabulated from both full survey datasets. Weighted Pearson product-moment correlations were used to summarize the relationships among BMI<sub>M</sub>, BMI<sub>SR</sub>, and the discrepancy (bias) between BMI<sub>M</sub> and BMI<sub>SR</sub> ( $BMI = BMI_M - BMI_{SR}$ ).

In the second stage, we estimated MR from independent models of BMI<sub>M</sub> and BMI<sub>SR</sub>, pointed out for which BMI categories the significance tests from BMI<sub>M</sub> and BMI<sub>SR</sub> models agreed or disagreed, then tested for bias in MR estimates. Weighted Cox proportional hazards regression models were fit to relate categorized BMI<sub>M</sub> and BMI<sub>SR</sub> separately to attained age mortality data with adjustments for covariates. We used counting process methods<sup>40</sup> to account for left-truncation in these data which sets the beginning of exposure for each participant to the age at which they entered the study. In separate subgroup analyses, we examined MR among ostensibly healthy subgroups of never-smokers at the time of survey (i.e., reported no major illnesses including acute myocardial infarction, heart failure, other heart problems, cancer, emphysema, or stroke).

In total, eight Cox models were fit. Each of the four datasets we analyzed ( $j = 1, \dots, 4$ : 1. NHANES II full survey, 2. NHANES II healthy never-smoker subgroup, 3. NHANES III full survey, and 4. NHANES III healthy never-smoker subgroup) were modeled twice: once with BMI<sub>M</sub> and again replacing BMI<sub>M</sub> with BMI<sub>SR</sub>. This produced eight sets of hazard ratio (HR) estimates; each individual HR representing the MR of one of the five BMI levels ( $i = 1, \dots, 5$ : 1. underweight, 2. normal weight, 3. overweight, 4. obese, or 5. severely obese) relative to the normal weight reference BMI level for the given model (e.g., the model of BMI<sub>SR</sub> in the NHANES II full survey). To help assess the MRs, we tabulated HR results from the eight models and indicated if the respective BMI<sub>M</sub> and BMI<sub>SR</sub> models agreed on the significance of the HRs at each BMI level within each of the four datasets. Note that, to save space in the table, we have omitted the HRs comparing the reference groups to themselves which will always have HR = 1. We tested for bias in the BMI<sub>SR</sub> MR estimates by computing 95% confidence intervals (CI) for the differences in BMI<sub>M</sub>-derived and BMI<sub>SR</sub>-derived HRs ( $\Delta HR_{ij} = HR_{ij}^{BMI_M} - HR_{ij}^{BMI_{SR}}$ ) at each BMI level,  $i$ , within each dataset,  $j$ . The variability in each  $HR_{ij}$  was computed by the delete-1 cluster jackknife method<sup>41</sup> of standard error estimation which takes into account the sampling design of NHANES II and III, respectively. Asymptotic  $\chi^2$  tests and t-tests were conducted by the delta method to infer significant differences<sup>42</sup>.

Data were analyzed using SAS v9.2 (SAS Institute, Cary, NC) and SAS-Callable SUDAAN v10.0 (Research Triangle Institute, Research Triangle Park, NC) to accommodate the complex multistage sampling design<sup>43</sup>.

## Ethical Approval

Institutional Review Boards of the University of Alabama at Birmingham, Thomas Jefferson University, and Johns Hopkins University approved the protocol.

## Results

Table 1 displays selected characteristics of the unweighted data from NHANES II and NHANES III. On average,  $BMI_M$  was about  $0.6 \text{ kg/m}^2$  larger than  $BMI_{SR}$ .

### Prefatory analysis of reporting bias

Participants belonging to the lowest and highest  $BMI_M$ -derived categories were misrepresented by  $BMI_{SR}$ -derived categories at the highest rates. BMI category misclassification rates from  $BMI_{SR}$  were low among those of normal weight with respect to underreporting (<2%) and over-reporting (<8%) for both surveys. The misclassification rates from over-reported  $BMI_{SR}$  among the underweight were high for both NHANES II (32%) and NHANES III (42%). Underreporting of  $BMI_{SR}$  lead to high misclassification rates for the obese and severely obese in NHANES II (35% and 34%) and NHANES III (35% and 31%). Even though misclassification rates were high in both NHANES II and III,  $BMI_M$  showed strong Pearson correlations with  $BMI_{SR}$  ( $r = 0.94$  in NHANES II;  $r = 0.95$  in NHANES III). Interestingly,  $BMI_M$  was moderately correlated with reporting bias ( $BMI = BMI_M - BMI_{SR}$ ) in both surveys ( $r = 0.36$  in NHANES II;  $r = 0.42$  in NHANES III), while  $BMI_{SR}$  showed little correlation with  $BMI$  ( $r = 0.02$  in NHANES II;  $r = 0.13$  in NHANES III).

### Analysis of mortality rate bias

HR estimates of MR relative to normal weight reference groups specific to the type of BMI ( $BMI_M$  or  $BMI_{SR}$ ) within both full survey datasets and the ostensibly healthy subgroups are illustrated in the two plots (Parts A and B) displayed in Figure 1. While the bias relationship between  $BMI_M$  and  $BMI_{SR}$  presented in the literature and our prefatory analysis might seem consistent and straightforward, its influence in biasing MR is complicated and inconsistent across survey waves and ostensibly healthy never-smoker subgroups. In Figure 1 Part A, for NHANES II, disparities in MR estimates ( $BMI_{SR}$  red lines vs.  $BMI_M$  blue lines) were largest among the ostensibly healthy participants (dashed lines) where, similarly to the full datasets,  $BMI_{SR}$  underestimated MR for the underweight and the severely obese, but overestimated MR for the overweight and the obese. In Figure 1 Part B, for NHANES III, the MR estimates for the healthy subgroup were smaller than those for the full dataset at each BMI level. The disparities in MR for the full NHANES III dataset appeared to have very similar magnitudes as for the ostensibly healthy of NHANES III at each BMI level, whereas the MR disparities for the full NHANES II dataset were not similar to those for the ostensibly healthy of NHANES II at the lowest and highest BMI levels.

Figure 1 shows that  $BMI_{SR}$  did not yield the same MR estimates as  $BMI_M$  for either the full datasets or healthy subgroups of NHANES II or III. Table 2 lists all these HR parameter estimates and accompanying significance test results. As such, the respective  $BMI_M$  and  $BMI_{SR}$  models disagreed on the significance of nearly half of the HR's computed. The  $BMI_M$  and  $BMI_{SR}$  models agreed on the *nonsignificance* of the HR parameter estimates for the obese and severely obese from the full NHANES II; the obese from the NHANES II healthy subgroup; the obese from the full NHANES III; and the overweight, obese, and severely obese from the NHANES III healthy subgroup.  $BMI_M$  and  $BMI_{SR}$  models agreed

on the *significance* of only the underweight HR parameter estimate from the full NHANES III dataset. BMI<sub>SR</sub> models detected significantly elevated MR among only the underweight (HR = 1.96,  $p < 0.01$ ) and overweight (HR = 0.85,  $p = 0.02$ ) from the full dataset of NHANES III.

Comparing HR estimates from the BMI<sub>M</sub> and BMI<sub>SR</sub> models, the HR<sub>*ij*</sub> estimates were statistically significantly different in the NHANES II full dataset ( $\chi^2 = 12.49$ ;  $p = 0.01$ ) and healthy subgroup ( $\chi^2 = 9.93$ ;  $p = 0.04$ ), but not in the NHANES III full dataset ( $\chi^2 = 5.63$ ;  $p = 0.23$ ) or healthy subgroup ( $\chi^2 = 1.52$ ;  $p = 0.82$ ). Table 3 provides the calculated HR<sub>*ij*</sub> estimates along with 95% CIs which indicate that the statistically significant differences were attributable to the overweight in the NHANES II full dataset analysis (HR<sub>31</sub> = -0.12; 95% CI: -0.19, -0.04;  $p = 0.002$ ) and the underweight in the NHANES II healthy subgroup analysis (HR<sub>12</sub> = 1.06; 95% CI: 0.01, 2.12;  $p = 0.032$ ).

## Discussion

NHANES II and III collected both measured and self-reported height and weight data and mortality follow-up affording the opportunity to empirically assess in nationally representative samples the extent to which substituting BMI<sub>SR</sub> for BMI<sub>M</sub> influences mortality results. Some have suggested that BMI-mortality results could be significantly affected by using BMI<sub>SR</sub><sup>16</sup> while others have suggested that no practical differences would result from its use<sup>33</sup>. We found that BMI<sub>SR</sub> was indeed highly correlated with BMI<sub>M</sub>, but there were systematic biases in reporting BMI (BMI) and high misclassification rates in both full surveys and their ostensibly healthy never-smoker subgroups. This misclassification of BMI, was sufficient to result in biased estimates of the BMI-MR association.

Using BMI<sub>SR</sub> in place of BMI<sub>M</sub> led to underestimation of mortality associated with the underweight in both surveys, the underweight of NHANES III, and the severely obese of NHANES II. However, BMI<sub>SR</sub> led to overestimation of mortality associated with the overweight in NHANES II, the obese of both surveys, and the severely obese of NHANES III. Moreover, hypothesis tests from the BMI<sub>M</sub> and BMI<sub>SR</sub> models did not agree for nearly half of the BMI HR parameter estimates. In particular, the models of BMI<sub>SR</sub> failed to detect six of the eight significant HR parameter estimates detected by BMI<sub>M</sub> models. Although we did not have statistical power to detect some fairly large differences, some MR discrepancies between the HR parameter estimates from the BMI<sub>M</sub> and BMI<sub>SR</sub> models (HR<sub>*ij*</sub>) were significantly different from zero among the overweight in the full NHANES II dataset, as well as the underweight in the healthy subgroup of NHANES II. After applying a Bonferroni adjustment to the significance level ( $\alpha = 0.003$ ) for the 16 HR<sub>*ij*</sub> t-tests, we found that the overestimated HR for the overweight of NHANES II remained significant ( $p = 0.002$ ). It is important to note that missing BMI (and other) values may have influenced our results and those of others. Investigating this additional source of bias is beyond the scope of this research, but may be an important topic for future research.

Although it is unclear why, the bias in terms of the magnitude (not the direction) of the underestimation or overestimation in MR parameter estimates between BMI<sub>SR</sub> and BMI<sub>M</sub>



models depended on whether we analyzed all subjects or only a subgroup of ostensibly healthy never-smokers at baseline. Interestingly, this may explain an apparent discrepancy in the literature. Specifically, some have found that the BMI-MR relationship appears to be roughly monotonically increasing and that overweight appears to increase MR, but primarily when one analyzes only ostensibly healthy never-smokers at baseline (e.g., <sup>13,14</sup>). In contrast, Flegal et al. <sup>16</sup> using BMI<sub>M</sub> found that restricting analyses only to ostensibly healthy never-smokers at baseline did not appear to make much difference in their essentially J-shaped association with MR and decreased MR of the overweight relative to the normal weight. Nevertheless, our results from the healthy never-smoker subgroup of NHANES II showed a nearly monotonically increasing trend in MR from the BMI<sub>SR</sub> model not replicated in the BMI<sub>M</sub> model of those data (see Figure 1 Part A). This suggests that the discrepancy could be at least partly attributable to the fact that the former analyses <sup>13,14</sup> used BMI<sub>SR</sub> whereas the latter <sup>16</sup> used BMI<sub>M</sub>. As an interesting side note, in light of findings of U- or J-shaped relationships between BMI and adverse outcomes, one may ask why there is often such a resistance to accept the suggestion that thinness is associated with increased health risk. Such findings are common, but are commonly attributed to ‘reverse causation’ - spurious associations with risk at low BMI levels resulting from weight loss caused by observable or latent disease conditions. While we have conducted analysis on ostensibly healthy never-smoker subgroups, it is unclear if, or to what extent, reverse causation may have influenced our results.

Many studies, including some which analyzed NHANES II <sup>26,27</sup> or III <sup>18,19, 22,23, 29</sup>, have compared self-reported height and weight with measured values <sup>17, 21, 24,25, 28, 30,32</sup>. They have found that misreporting height and weight might be systematically influenced by BMI<sub>M</sub> <sup>24,25, 27,30</sup>, gender <sup>21,25, 27,29, 31</sup>, age <sup>18, 22, 24,25, 27,32</sup>, race/ethnicity <sup>19, 27,29</sup>, disease or health status <sup>30,31</sup>, smoking history or health behaviors <sup>29</sup>, and end-digit preference <sup>24, 27</sup>. Some have also noted dependencies based on geographic region <sup>18</sup> and socioeconomic variables <sup>24, 28,29</sup>. Relatively few studies have pronounced self-reported height and weight to be a valid and sufficient proxy for measured height and weight <sup>21, 23, 32</sup>. Others caution against relying on BMI<sub>SR</sub> <sup>22, 24, 29</sup>, particularly for estimating relationships between BMI and health outcomes <sup>26</sup>. This includes obesity-related outcomes which seem correlated with misreporting, such as diabetes or hypertension <sup>30</sup>. Many more studies have compared measured vs. self-reported height, weight, and BMI in the US and other countries. For systematic review of these studies, see <sup>44</sup>.

Some investigators have suggested that adjusting BMI<sub>SR</sub> can help in studies lacking measurements <sup>17, 25, 28, 32, 45</sup>. Although highly correlated with BMI<sub>M</sub>, BMI<sub>SR</sub> was not linearly related with reporting bias ( BMI). Our results agreed with those of others <sup>26</sup> that BMI does not appear to be recoverable from BMI<sub>SR</sub>. Thus, BMI<sub>SR</sub> should not be considered a reliable source of information for estimating BMI<sub>M</sub> with a regression model. This calls into question the validity of methods using self-reported heights and weights and other study variables, such as the methods proposed by Stommel and Shoenborn <sup>28</sup> based on recent NHANES data, to generate corrected BMI scores conditioned on BMI<sub>SR</sub>. When we applied their method <sup>28</sup> to NHANES III, although the corrected BMI scores did improve classification over uncorrected BMI<sub>SR</sub> among the severely obese (increased sensitivity from 68% to 84%), they seriously exacerbated the misclassification problems among the

underweight, normal weight, overweight, and obese (sensitivity decreased from 58%, 91%, 80%, and 62% to 3%, 30%, 31%, and 47%, respectively). Compared to  $BMI_M$ , the corrected BMI scores also increased the bias in estimating MR beyond that which we showed from using  $BMI_{SR}$ . It remains unclear, however, if future studies of BMI and mortality relying on  $BMI_{SR}$  would benefit in some way from the application of measurement error correction methods<sup>46-48</sup>.

In a related context, Chiolero et al.<sup>49</sup> presented a hypothetical data example of how obesity and health condition association estimates can be overestimated as a result of systematic misclassification of BMI from using  $BMI_{SR}$ . However, they made several assumptions which may not hold in human data and hypothetical data such as they presented can just as easily be simulated to show how risk estimates can be underestimated or completely obscured depending on the underlying association between variables, outcomes, and the error distribution of the data generated. James et al.<sup>20</sup> suggested that, relative to  $BMI_M$ , the narrower distribution of  $BMI_{SR}$  could result in artificially steep slopes for linear associations with continuous outcomes. Rothman<sup>50</sup> indicated that this could be true for BMI and mortality, but in their hypothetical example, like Chiolero et al.<sup>49</sup> they assumed that the association would be linearly increasing and that the misreporting errors would be nondifferential. These assumptions do not likely hold for mortality considering that linearity is not generally found in  $BMI_M$ -mortality data<sup>11, 15</sup> and differential reporting bias could stem from latent or diagnosed disease conditions influencing height and weight self-reporting patterns<sup>30</sup> and MR<sup>2</sup>. Thus, it is reasonable to expect that the MR results from using  $BMI_{SR}$  could be biased in either direction.

The selection processes between the aforementioned  $BMI_{SR}$  studies<sup>9-10, 13-14</sup> and the  $BMI_M$  studies<sup>11, 15</sup> might also account for some disparities in their results. NHANES used complex multistage sampling to provide a cost-effective way to capture and examine a relatively small cohort that, when properly analyzed, is expected to represent well the US non-institutionalized population. This design does not preclude the potential for sampling bias. With the notable exception of the National Health Interview Survey (NHIS), large mortality follow-up data sources relying on  $BMI_{SR}$  have not been constructed in this manner. For example, the Nurses' Health Study applied its resources toward collecting reported information from a very large occupational cohort of nurses. This cohort should represent well the population of middle-aged nurses, but probably not the same population as NHANES. Additionally, having provided informed consent, the participants of NHANES II and III presumably knew that their height and weight would be measured subsequent to their report of it. In contrast, the participants in most studies providing self-reports would not expect their height and weight to be verified by measurements which has been shown to lead to greater biases in the self-reported values<sup>17</sup>. It may follow that biases in MR estimation may be greater in typical studies relying on  $BMI_{SR}$  from participants who know that their weight and height will not be checked.

While we acknowledge the power of  $BMI_{SR}$  in large-scale epidemiologic investigations of MR, we conclude that  $BMI_{SR}$  should not be treated as interchangeable with  $BMI_M$ . The bias introduced into MR estimation and inference with  $BMI_{SR}$  appears to play an important role in explaining the disparate BMI-mortality relationships reported. We observed the greatest



reporting bias in the BMI categories having the smallest proportion of participants (i.e., 2% were underweight and 5%-8% were severely obese). Since the prevalence of people in each BMI level changes over time, even if the relationship between BMI<sub>M</sub> and BMI<sub>SR</sub> stays the same, mortality HRs could be biased differentially across BMI categories. Thus, even small changes in the BMI distribution in future studies could have dramatic effects on misclassification rates which could assert similarly dramatic, possibly erratic, effects on MR estimates when BMI<sub>SR</sub> is used in place of BMI<sub>M</sub>. Further investigation is necessary to determine if BMI<sub>SR</sub> is a reliable substitute for BMI<sub>M</sub> in the analysis of other health outcomes.

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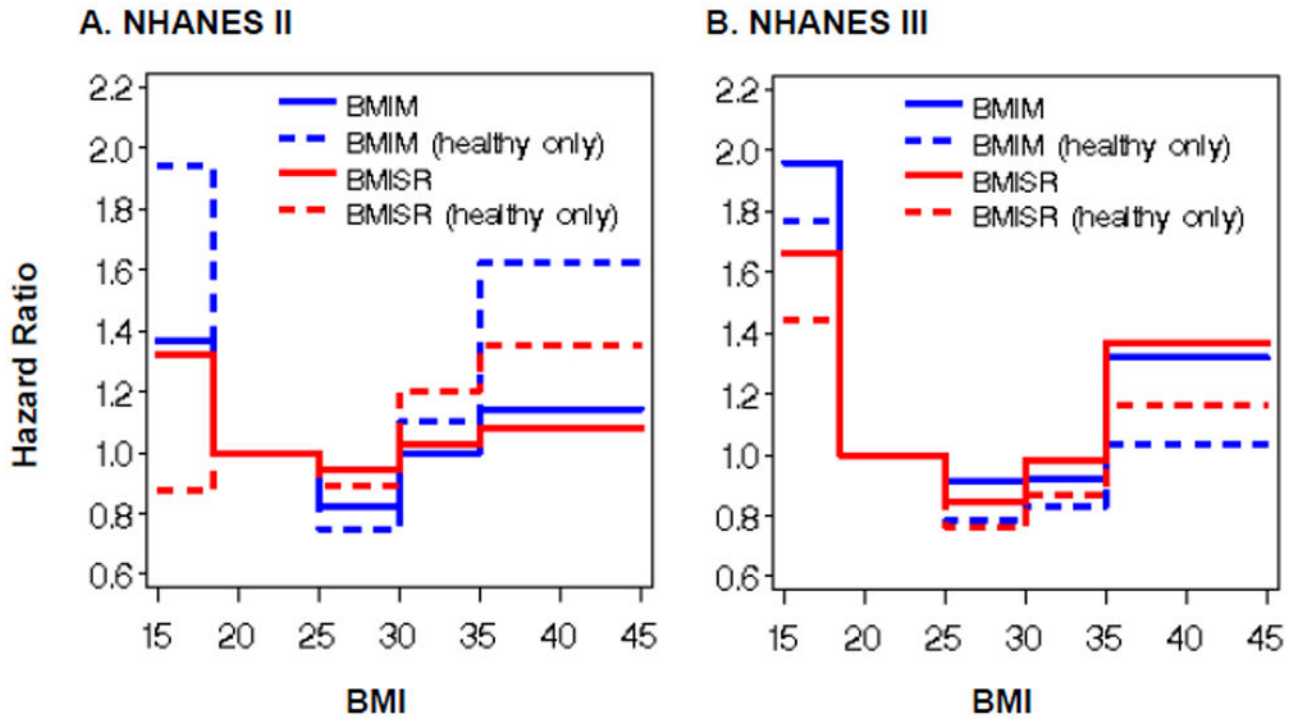
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**Figure 1. Parts A-B. Weighted mortality hazard ratios by  $BMI_M$  and  $BMI_{SR}$**

Scheme for associating RNA sequence features with splicing outcomes. Top left: More than 1000 diverse features were used; the examples shown here were chosen to illustrate their diversity. Each feature was also defined by the region in which it occurs, as indicated on the map on the lower left, where the alternatively spliced exon is red. Upper right: Exon inclusion data were originally measured in 27 mouse tissues or cell lines using microarrays and then consolidated into four tissue types: C, central nervous system; M, striated and cardiac muscle; D, digestion related tissues; E, embryonic tissue and stem cells. A machine learning algorithm was devised to associate particular features with particular splicing outcomes; the latter being categorized as increased exon inclusion, increased exon exclusion, or no difference in comparing two tissue types. After training on a set of ~3000 exons, the algorithm was able to reliably predict these splicing outcomes in a set of test exons.

**Table 1**  
**Unweighted demographic and mortality information: means (with standard deviation) or counts (with percentage)**

	NHANES II		NHANES III	
	Full Dataset	Healthy* Subgroup	Full Dataset	Healthy* Subgroup
<b>Sample size</b>	9 227	3 022	15 060	6 141
<b>Women</b>	4 878 (53.0)	2 146 (71.0)	7 937 (52.7)	4 094 (66.7)
<b>Age</b>	54.9 (13.3)	54.8 (13.8)	52.7 (18.4)	49.9 (18.6)
<b>Healthy*</b>	3 022 (32.8)	3 022 (100)	6 141 (41.0)	6 141 (100)
<b>BMI<sub>M</sub></b>	26.1 (5.0)	26.6 (5.3)	27.3 (5.8)	27.7 (6.1)
<b>BMI<sub>SR</sub></b>	25.5 (4.6)	25.8 (4.8)	26.7 (5.4)	26.9 (5.5)
<b>BMI</b>	0.6 (1.7)	0.7 (1.8)	0.6 (2.0)	0.8 (2.1)
<b>Deaths</b>	2 143 (23.2)	450 (14.9)	2 820 (18.7)	741 (12.1)
<b>Follow-up</b>	13.3 (3.6)	14.0 (2.8)	8.2 (2.6)	8.4 (2.2)

\* The ostensibly “healthy” subgroup consists of never smokers having reported no history of acute myocardial infarction, heart failure, other heart problems, cancer, emphysema, or stroke.

**Table 2**  
**Mortality hazard ratios: do the BMI<sub>M</sub> and BMI<sub>SR</sub> significance test results agree?**

		BMI Type	HR*	p-value	Significant at $\alpha = 0.05$ ?	Do the tests agree?
NHANES II	Underweight	BMI <sub>M</sub>	1.37	0.04	Yes	No
		BMI <sub>SR</sub>	1.32	0.07	No	
	Overweight	BMI <sub>M</sub>	0.82	<0.01	Yes	No
		BMI <sub>SR</sub>	0.94	0.30	No	
	Obese	BMI <sub>M</sub>	1.00	1.00	No	Yes
		BMI <sub>SR</sub>	1.03	0.82	No	
	Severely Obese	BMI <sub>M</sub>	1.14	0.25	No	Yes
		BMI <sub>SR</sub>	1.03	0.67	No	
	Underweight	BMI <sub>M</sub>	1.94	0.03	Yes	No
		BMI <sub>SR</sub>	0.87	0.71	No	
	Overweight	BMI <sub>M</sub>	0.75	0.02	Yes	No
		BMI <sub>SR</sub>	0.89	0.35	No	
Obese	BMI <sub>M</sub>	1.10	0.56	No	Yes	
	BMI <sub>SR</sub>	1.20	0.37	No		
Severely Obese	BMI <sub>M</sub>	1.63	0.02	Yes	No	
	BMI <sub>SR</sub>	1.35	0.24	No		
Underweight	BMI <sub>M</sub>	1.96	<0.01	Yes	Yes	
	BMI <sub>SR</sub>	1.66	<0.01	Yes		
Overweight	BMI <sub>M</sub>	0.91	0.21	No	No	
	BMI <sub>SR</sub>	0.85	0.02	Yes		
Obese	BMI <sub>M</sub>	0.92	0.26	No	Yes	
	BMI <sub>SR</sub>	0.98	0.85	No		
Severely Obese	BMI <sub>M</sub>	1.32	0.02	Yes	No	
	BMI <sub>SR</sub>	1.37	0.07	No		
NHANES III	Full Dataset					



	BMI Type	HR*	p-value	Significant at $\alpha = 0.05$ ?	Do the tests agree?
Underweight	BMI <sub>M</sub>	1.77	0.02	Yes	No
	BMI <sub>SR</sub>	1.44	0.11	No	
Overweight	BMI <sub>M</sub>	0.78	0.06	No	Yes
	BMI <sub>SR</sub>	0.76	0.06	No	
Obese	BMI <sub>M</sub>	0.83	0.19	No	Yes
	BMI <sub>SR</sub>	0.86	0.43	No	
Severely Obese	BMI <sub>M</sub>	1.03	0.89	No	Yes
	BMI <sub>SR</sub>	1.17	0.57	No	

\* HR values represent mortality hazard relative a normal weight reference group that is specific to the type of BMI (BMI<sub>M</sub> or BMI<sub>SR</sub>) in each of the four datasets. The HRs for the normal weight reference groups have been omitted as the HRs will always be 1.

**Table 3**  
**Differences in hazard ratios\* : BMI<sub>M</sub> vs. BMI<sub>SR</sub> (with 95% CI)**

BMI Category	NHANES II		NHANES III	
	Full dataset	Healthy subgroup	Full dataset	Healthy subgroup
<b>Underweight</b>	0.05 (-0.19,0.28)	1.06 (0.01,2.12) <sup>†</sup>	0.30 (-0.10,0.71)	0.32 (-0.48,1.13)
<b>Overweight</b>	-0.12 (-0.20,-0.05) <sup>‡</sup>	-0.14 (-0.30,0.02)	0.06 (-0.02,0.15)	0.02 (-0.13,0.18)
<b>Obese</b>	-0.03 (-0.19,0.14)	-0.10 (-0.45,0.25)	-0.06 (-0.20,0.06)	-0.03 (-0.30,0.23)
<b>Severely Obese</b>	0.06 (-0.20,0.33)	0.28 (-0.23,0.78)	-0.05 (-0.34,0.25)	-0.13 (-0.48,0.21)

\*  $HR_{ij}$ , the difference in HR from a model with BMI<sub>M</sub> vs. a model with BMI<sub>SR</sub> ( $HR_{ij}^{BMI_M} - HR_{ij}^{BMI_{SR}}$ ) for the *i*<sup>th</sup> BMI category in the *j*<sup>th</sup> dataset (or subgroup).

<sup>†</sup> p = 0.033

<sup>‡</sup> p = 0.002