Clarifying methodological misunderstandings regarding estimates of excess mortality associated with elevated body weight

Zachary J. Ward,[a]* Walter C. Willett,[b,c] and Steven L. Gortmaker [d]

[a]Center for Health Decision Science, Harvard T.H. Chan School of Public health, 718 Huntington Ave, Boston, MA 02115, USA
[b]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[c]Department of Epidemiology, Harvard T.H. Chan School, Boston, MA, USA
[d]Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, MA, USA

The rise of obesity in the US has been well-documented,[1,2] and a large body of scientific evidence has linked elevated body mass index (BMI) with increased risk of many diseases[3,4] and all-cause mortality.[5] We recently published updated estimates of excess mortality associated with elevated body weight in the US, finding that in 2016, excess weight was responsible for nearly 500,000 deaths and a loss of life expectancy of nearly 2.4 years, with large disparities by state and demographic group.[6]

However, a letter to the editor from Dr. Flegal asserts that our findings may overestimate BMI-related excess mortality, claiming that our method to adjust for BMI self-report bias "does not reduce systematic error in self-reported BMI", and that hazard ratios relating BMI to all-cause mortality based on a global pooling dataset may be inappropriate for our analysis.[7] We wish to clarify these points as these comments are inaccurate and misleading.

First, Dr. Flegal misrepresents our adjustment method for BMI self-report bias. It is well-known that self-reported BMI substantially underestimates obesity prevalence and needs to be corrected.[8] We developed a semi-parametric method to adjust self-reported BMI by quantile, and have shown that this produces adjusted BMI distributions statistically similar to measured BMI in the National Health and Nutrition Examination Survey (NHANES) — the 'gold standard' for obesity measurement in the US.[2] Furthermore, using cross-validation with NHANES data, we have demonstrated that this method, applied by sex and age group, produces unbiased estimates of mean BMI and obesity prevalence, both overall and by various subgroups.[9] The claim that this method fails to address systematic error has thus

been empirically shown to be false. However, no reference is made to this published work in the letter.

We are also not aware of any evidence for the speculative assertion that this method "may overestimate the prevalence of the highest BMI category", and no reference is provided for this statement. Instead, we have previously shown that regression-based approaches to bias-correction underestimate the variance of the BMI distribution, thus underestimating the prevalence of high BMI categories.[10] In contrast, our method was developed to adjust the entire distribution so that it is statistically similar to measured BMI, thus appropriately capturing the tails of the BMI distribution.

It is true that, as with any method, our approach relies on certain assumptions, and we would welcome constructive criticism regarding how this method could potentially be improved. However, the comments from Dr. Flegal provide no such suggestions, nor propose any alternative method of bias-correction.

Second, the comments regarding our use of mortality hazard ratios indicate a misunderstanding of our approach. We did not use the estimates from the global pooled dataset[5] directly in our model, but used them to set prior probability distributions for the general relationship between mortality and BMI categories by age group. These parameters were then calibrated to US-specific data on all-cause mortality rates. This approach is described in the Methods of our manuscript, where we state, "Although we set priors for the hazard ratios using global estimates, we fitted the model parameters to US-specific mortality data by sex, race/ethnicity, age group, and state, allowing us to estimate subgroup-specific hazard ratios which are consistent with empirical mortality rates."[6]

Model calibration thus revises these prior estimates so that they produce all-cause mortality estimates consistent with data for over 60,000 demographic groups in the US, accounting for trends in BMI and smoking.[6] We also demonstrate that our approach has high predictive accuracy for all-cause mortality rates among a randomly sampled test set of (US-specific) data not used to calibrate the model.[6] The claim that hazard ratios from the global dataset were simply 'combined' with adjusted

---

Comment

BMI values ignores the extensive model calibration process which comprised the majority of our work for this analysis.

Our estimates of weight-associated excess mortality are indeed higher than previous estimates, but this was expected given that our study uses more recent data with higher obesity prevalence, and also estimates mortality associated with any excess weight (BMI greater than 'optimal' BMI), not just obesity (BMI ≥30). Furthermore, our individual-level model (which accounts for the joint distribution of demographic variables and smoking) uses a continuous approach to model (age-specific) BMI hazard ratios, and models the location of 'optimal' BMI as a random variable. Therefore, our results are not sensitive to categorical threshold effects, or the choice of a specific reference group, which can be especially problematic if this group is impacted by reverse causation (i.e., health conditions which both increase mortality risk and decrease BMI).

Indeed, as we acknowledge in the manuscript, although we control for smoking and age, our estimates may be influenced by residual impacts of reverse causation and frailty, especially at older ages.[6] Therefore, because our estimates of adjusted obesity prevalence are unbiased, and our hazard ratios (fitted to empirical US-specific data) may be underestimated, our estimates of excess weight-related mortality may be conservative.

Contributors
ZJW wrote the original draft. All authors contributed to the review and editing of the manuscript.

Declaration of interests
None.

References
1 Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA*. 2016;315(21):2284–2291.
2 Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. state-level prevalence of adult obesity and severe obesity. *N Engl J Med*. 2019;381(25):2440–2450.
3 Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer — viewpoint of the IARC working group. *N Engl J Med*. 2016;375(8):794–798.
4 Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and cardiovascular disease: a scientific statement from the American heart association. *Circulation*. 2021;143(21):e984–e1010.
5 Collaboration Global BMI Mortality, E Di Angelantonio, Bhupathiraju S, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet*. 2016;388(10046):776–786.
6 Ward ZJ, Willett WC, Hu FB, Pacheco LS, Long MW, Gortmaker SL. Excess mortality associated with elevated body weight in the USA by state and demographic subgroup: a modelling study. *EClinicalMedicine*. 2022;48:101429.
7 Flegal KM. Excess mortality estimates may be too high. [Letter submitted to EClinical Medicine].
8 Connor Gorber S, Tremblay M, Moher D, Gorber B. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. *Obes Rev*. 2007;8(4):307–326.
9 Ward ZJ, Gortmaker SL. A rigorous evaluation of a method to adjust BMI for self-report bias. *Obesity (Silver Spring)*. 2022;30(2):284–285.
10 Ward ZJ, Long MW, Resch SC, et al. Redrawing the US obesity landscape: bias-corrected estimates of state-specific adult obesity prevalence. *PLoS One*. 2016;11:e0150735.