Review

MOLECULAR METABOLISM

Mortality rate and overweight: Overblown or underestimated? A commentary on a recent meta-analysis of the associations of BMI and mortality

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ABSTRACT

In this review, we discuss strengths and limitations of a recent rigorous systematic review and meta-analysis of the literature on associations of all-cause mortality with overweight and obesity. A perspective on its meaning and potential implications are provided. To move this field forward, we suggest modeling BMI as a continuous variable, switching to modeling longevity instead of mortality, and generating large publicly available datasets in broad and diverse populations for discerning the extent to which the BMI–mortality relationship differs between groups and over time. Randomized studies of obesity-related interventions that provide assessments of their actual effects on lifespan or mortality would have great value for helping to establish valid clinical and public health recommendations around weight loss and mortality.

Keywords Mortality; Obesity; Overweight; BMI

1. INTRODUCTION

In their rigorous systematic review, published in the *Journal of American Medical Association*, Flegal et al. [1] integrated the available literature on the associations of all-cause mortality with overweight and obesity using all studies that met their inclusion criteria. They meta-analyzed results from 97 studies having reported mortality hazard ratios (HRs) for some, or all, of the following standard body mass index (BMI: kg/m^2) categories: normal weight ($18.5 - < 25$), overweight ($25 - < 30$), grade 1 obesity ($30 - < 35$), and grades 2 and 3 obesity (BMI$\geq$35). In total, they analyzed HRs representing over 2.88 million people and concluded that, in comparison to normal weight, obesity grades 2 and 3 were associated with increased mortality, while obesity grade 1 was not. They also found that overweight was associated with decreased mortality. Herein, we discuss strengths and limitations of this study and provide a perspective on its meaning and potential implications.

2. DID THE AUTHORS' PROCEDURES ADEQUATELY CHARACTERIZE THE ASSOCIATIONS THAT EXIST?

Including studies relying on BMI from self-reported height and weight (BMI_{SR}) was a two-fold strength of the meta-analysis. It increased the number of studies in the systematic review by roughly 50% and provided valuable insights on how results from measured BMI (BMI_M)–mortality studies compare with BMI_{SR}–mortality studies. However, Flegal et al. [1] did not discuss how self-reporting errors may have depended on unmeasured or unadjusted confounders related to mortality. At least one study [2] showed an impact on mortality associations from this differential reporting error bias in nationally representative data on US adults from the National Health and Nutrition Examination Survey (NHANES) data where both BMI_M and BMI_{SR} were available. The reporting errors in the meta-data could similarly be expected to bias BMI_{SR}–mortality associations both upwardly or downwardly and give the results greater heterogeneity, error variance, and bias compared to results from using BMI_M.

Indeed, the study inclusion criteria chosen by Flegal et al. [1] were broad. This suggests that the results from their meta-analysis might broadly represent the general population. Their criteria were also exclusive enough so that many HRs were controlled for at least age, gender, and smoking while avoiding HRs diluted by over-adjustment for variables in the causal pathway between BMI and mortality. Perhaps, though, the included studies did not adjust well enough for potential sources of confounding and effect modification. Previously, Flegal et al. [3] used age as time scale and determined that, based on BMI_M from the first three waves of NHANES, the proportional hazards assumption was not met across attained ages and that the impact of obesity on mortality may have decreased over time. To address lack of proportionality, they allowed the categorical BMI-mortality HR parameters to depend on age by stratifying models by attained age groups (< 60, $60 - < 70$, and $\geq$70 years) and indicated that the impact of overweight and obesity on mortality attenuates with age. Even though age

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at BMI assessment was apparently used in the originally published studies to adjust the included HRs and the meta-analysis was stratified by the age range of the individual study cohorts, this may not have been sufficient to correct for biases introduced by meta-analyzing time-fixed estimates of what were likely age-dependent HRs. In addition, the meta-analysis was not adjusted for the varying calendar time of the studies included in the analysis. This could have biased the meta-estimates as a function of the distribution of calendar time across studies. Some might argue that analyses of data including ever-smokers or those diagnosed with certain illnesses (e.g., cancer or cardiovascular diseases) are flawed since these factors are so strongly related to both weight loss and early mortality. The trade-off for limiting analyses to subgroups, in an attempt to improve 'internal validity' or confidence in a presumed causal inference, is that they produce results of limited generalizability. It remains unclear if subgroup analyses in this context actually do improve validity and, if so, where the balance might be struck, between model adjustments and subgroup analyses, to optimize validity and generalizability.

While the authors suggest that using BMI categories improves comparability of results between prospective mortality studies utilizing BMI assessments at a single initial point (as opposed to as time-varying covariates), it also impairs the ability to compare those results to results from studies of longitudinal BMI assessments. To analyze longitudinal changes in BMI, unit changes or transitions between narrow categories may be used to correlate how weight gain or weight loss relates to mortality. The wide-ranging BMI categories meta-analyzed would be of limited use in studies of weight changes because the likelihood of a given individual making a transition between BMI categories depends on how close that individual is to the respective boundary for that transition. The experiences and mortality associated with someone overweight at BMI = 25 having transitioned to grade 1 obesity might be quite different from that of an otherwise similar overweight person at BMI = 29 making the same transition over the same time period. Modeling of the continuous nonlinear, U-shaped, possibly dynamic functional BMI–mortality relationship could help address this by providing more accurate estimates and important information about how BMI–mortality results from data having a single BMI assessment per person might be translated to longitudinal BMI change–mortality results. However, it might cost in terms of comparability between studies because of the many alternative approaches available for characterizing the shape of the association observed—the results of which could be impossible to meta-analyze effectively without the raw data.

Karl Popper once wrote "Science may be described as the art of systematic over-simplification—the art of discerning what we may with advantage omit." [4]. Though we have noted some complexities in the estimation of the BMI–mortality association, we nevertheless agree that, at the level of complexity at which they constructed their estimates, Flegal et al. [1] provided a reasonable characterization of the BMI–mortality association.

3. DO THE OBSERVED ASSOCIATIONS ADEQUATELY REPRESENT THE CAUSAL EFFECTS OF BMI ON MORTALITY?

Stating that Flegal et al.'s findings [1] characterize the association of BMI categories with mortality to a reasonable degree is different from discussing causation. The findings reported by Flegal et al. are associations ('correlations') between BMI categories and relative mortality rates that have been adjusted for some potential confounding variables. Such associations, like all associations, may or may not represent causation. We all know the classic phrase "correlation does not imply causation." Notably, it is equally true, that "lack of correlation does not imply lack of causation."

One might argue that isolating the causal effects of BMI on mortality with definitive certainty may be impossible, because men and women cannot be randomly assigned to have a particular BMI level to determine its effect on longevity. As such, the results of any observational BMI–mortality study (whether BMI was assessed at a single time or longitudinally) cannot be explicitly verified. Regardless of the study design, we cannot determine with certainty if the differences in BMI between study participants caused differences in the lengths of their lives. Yet, despite this fact, observational studies have provided important information.

Few experts doubt that the association of the higher levels of obesity with increased mortality indicates that a high level of obesity causes increased mortality. This interpretation is consistent with an overwhelming body of corroborative evidence [5]. On the other hand, many conjecture that the observed associations may underestimate the true causal effect. The primary hypothesis underlying this conjecture is that extant health status confounds the relationship between BMI and mortality. Specifically, it seems that healthier people have a greater tendency to gain weight and less healthy people a greater tendency to lose weight. Coupled with the fact that healthiness is presumably positively related to longevity, this all suggests that the deleterious effects of higher BMIs are likely underestimated [6].

Similarly, though there is no doubt that some body fat is essential [7] and no doubt that some level of BMI is too low [8], thereby implying that there must be a concave upward ('bathtub shaped') causal curve between BMI and mortality, whether the base of the causal curve is the same as the base of the association curve remains the subject of debate. We believe the base of the causal curve is likely lower than the base of the observed association curve due to confounding by underlying aspects of health that cannot be fully observed and controlled for in analyses. We believe this is the most parsimonious explanation for a wide collection of observations from epidemiology, clinical trials, and experimental model organism research. But, but we cannot unequivocally prove our view any more than someone who believes that the observed association curve does adequately represent the causal curve can prove the correctness of that view.

4. ARE THE FINDINGS REALLY THAT NEW AND SURPRISING?

The most controversial findings of the meta-analysis were that, relative to being normal weight, grade 1 obesity was not associated with elevated mortality and overweight was associated with significantly lower mortality. Several editorials (e.g., [9]) were critical of certain aspects of the meta-analysis, suggesting, among other things, that using a wide-ranging normal weight reference group that contained a heterogeneous group of people (e.g., physically active, smokers, those with cancer or other conditions that cause weight loss, frail elderly people) may have produced biased findings that are misleading for people interested in what constitutes a healthy or optimal weight. Although the absence of a deleterious association between grade 1 obesity and mortality is somewhat novel, many previous studies (e.g., [10–13]) have found overweight is not associated with increased mortality and in some cases with decreased mortality. From a public health perspective, it is not hard to imagine that the aggressive management of obesity-related co-morbidities has, over time, served to attenuate the magnitude of both the overweight- and grade 1 obesity–mortality associations.

Flegal et al.'s findings [1] in no way suggest that overweight and grade 1 obesity are not serious health concerns. Some commentators have criticized Flegal et al. on those grounds, but that is a misguided criticism as Flegal et al.'s meta-analysis was not about general health, it was only

about mortality. Clearly one can live a long life marked by suffering, disability, and illness and there is some evidence that such is often the outcome of obesity [14]. So, we should not be cavalier about the effects of overweight or grade 1 obesity on health and quality of life, and Flegal et al.'s analyses do not suggest otherwise.

5. SOME SUGGESTIONS FOR GOING FORWARD

There are many things we can do to move this field forward. First, with respect to the conduct and analysis of observational epidemiologic studies, there can be many improvements made in measurement, including using better measures of body composition [15]. Modeling BMI as a continuous variable rather than in categories is more informative and subject to fewer biases [16]. Although we, like Flegal et al., sometimes use BMI as a categorical variable to make our results comparable to others, in the long run we think it will be best to always model BMI as a continuous variable, and use 'knotted' regressions, if such methods can be refined and made more accessible, as they provide a hybrid of the best features of continuous and categorical modeling [17]. Switching to modeling longevity per se, as opposed to hazard ratios (for example by switching to parametric survival analyses), offers a method of analyzing BMI and mortality data that produces results which are, in many cases, more interpretable for most non-statisticians (and even for many statisticians) than are hazard ratios [18]. Finally, large datasets in broad and diverse populations need to continue to be generated, made publically available, and analyzed so we may better discern the extent to which the BMI–mortality relationship differs between groups and over time [19].

There is also a clear need for randomized studies of obesity-related interventions intended to increase lifespan and an assessment of their actual effects on lifespan or mortality. Such studies have begun to emerge (e.g., [20]), but several that were planned were discontinued (e.g., [21]) for various reasons. Hence, though the model organism data are quite supportive [22], we do not yet have convincing data from *randomized controlled trials* in humans that methods used for promoting weight loss among obese persons prolong life. Although such trials cannot unambiguously separate the effects of a weight loss treatment on longevity from the effects of weight loss per se on longevity [23], such trials would nevertheless have great value for helping to establish valid clinical and public health recommendations around weight loss and mortality.

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CONFLICT OF INTEREST

None declared.

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