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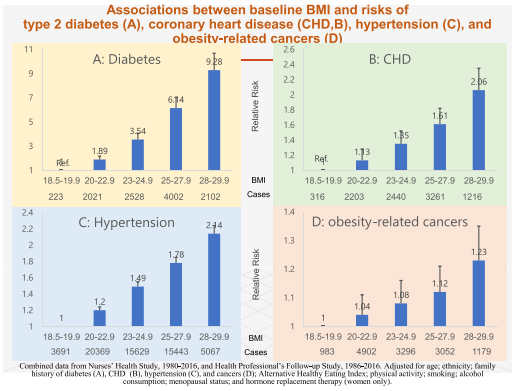
Evidence does not support benefit of being overweight on mortality



To the editor:

In her recent personal account,[1] Flegal discusses criticism of her previous work, including the 2013 meta-analysis of BMI and mortality suggesting that being overweight (BMI 25 to <30 kg/m2) was associated with significantly lower mortality than being normal weight and that grade I obesity (BMI 30 to <35 kg/m2) was not associated with excess mortality.[2] Unfortunately, that meta-analysis based on published studies[2] did not deal adequately with the facts that smokers have lower BMI's but high mortality, that people with serious disease often lose weight before they die, and that elderly people frequently lose lean mass as part of a downward frailty spiral to death. These are not statistical issues, but rather the reality of human biology and require detailed analyses that could not be conducted adequately in the meta-analysis of previously published data. These biological causes of weight change mean that short term predictions of mortality suggest lower risk in those who are overweight, but this is an artifact of these biases. Once these are recognized and accounted for simultaneously, both overweight and all levels of obesity are clearly associated with excess mortality. These sources of bias have been known for many years.[3] Confounding by cigarette smoking and weight loss related to chronic illness can be profound and intractable; thus, optimal analyses of the BMI-mortality relationship have been conducted in nonsmokers and those without cancer or other major illnesses at enrollment. Because of these intractable biases, analyses of body weight and mortality among smokers will not be interpretable and data from this increasingly small subgroup should not contaminate the findings among nonsmokers.

Flegal[1] also does not acknowledge the massive and incontrovertible evidence that both overweight and obesity are linked to elevated risks of type 2 diabetes, hypertension, dyslipidemia, heart disease, stroke, several types of cancer, and myriad other health conditions that are among the leading causes of premature death[4,5] (e.g. see figure for BMI range of 18.5 to <30). Importantly, Flegal[1] neglected to discuss the far larger meta-analysis including 30.3 million persons that clearly showed the lowest mortality was below a BMI of 25 when confounding due to smoking and reverse causation due to underlying disease were minimized and addressed simultaneously.[6] This meta-analysis was ten times larger than that of Flegal et al.[2] largely because the latter excluded many of the larger and more informative cohorts simply because they used finer categorization of BMI, which was possible and appropriate because of their larger size. Also not discussed was the large Mendelian randomization analysis[7] showing the lowest mortality is below a genetically determined BMI of 25, and that any excess mortality at the lowest BMI's was limited to smokers. Further, the very large global collaborative analysis of primary, individual-level, data from multiple studies, including 239 cohorts with 10.6 million participants and 61 experienced statisticians and epidemiologists from many institutions as co-authors, firmly refuted the Flegal et al. meta-analysis' conclusions regarding overweight and obesity.[8] The availability of individual-level data in the collaborative analysis allowed detailed examination of sources of bias, that were not possible with summaries of the published studies, such as simultaneous stratification by age and smoking. Separate analyses of cohorts with self-reported and measured BMI showed similar results. The study concluded that "The associations of both overweight and obesity with higher all-cause mortality were broadly consistent in four continents. This finding supports strategies to combat the entire spectrum of excess adiposity in many populations." That study was also preceded by an analysis of individual level data from multiple cohorts including 1.4 million participants coordinated by the U.S. National Cancer Institute (NCI) in response to issues raised by Flegal; this analysis came to the same conclusions as global collaborative analysis regarding BMI and mortality,[9] again refuting Flegal's conclusions about overweight and grade 1 obesity.

Timely critiques and public debate of the Flegal et al. studies, which did not involve *ad hominin* criticism, were appropriate because the misleading conclusions were being widely promoted in the mass media[10] and by advertisements of the food and beverage industries (https://www.consumerfreedom.com/downloads/ads/print/print_obesity_hype.pdf), and because those conclusions had direct potential implications for personal health decisions, clinical practice, national guidelines, and public policy.

Although analyses of BMI and mortality are important, clinical guidelines should also take into account the data on chronic disease incidence and morbidity burden, as noted above,[4,5] which add to the evidence on harms of major weight gain and excess body fat. Moreover, every five years, the US Dietary Guidelines Advisory Committees have considered the evidence on a wide range of health consequences of obesity and have recommended maintaining healthy weight through diet and exercise as a cornerstone of Dietary Guidelines for Americans. At a time when the distribution of BMIs continues to shift to higher levels in the US and thereby contributes to recent reductions in life expectancy, it is critical to use the best available data to inform clinical guidelines and public policies for obesity prevention and control. Misleading data on obesity and mortality cause public confusion and may undermine policies and public health efforts to address overweight and

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obesity. We also note that in counseling individual patients, weight gain and assessment of body fat distribution, such as abdominal circumference, should be considered in addition to current BMI. Further, prevention of weight stigmatization and eating disorders is also important.

We agree with Flegal that recommendations need to be based on unbiased data, and that has been the goal of the pooled analyses of individual level data in the global collaborative analysis and the NCI cohort consortium. To curb the obesity epidemic, it is critical to address both individual level and population level factors (e.g. food environment) and focus on prevention and improving overall wellbeing and quality of life.

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