



Letters to the Editor

Does the optimal BMI really vary by age and sex?

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Yi *et al.* show convincingly in a large cohort of 12.8 million adults that the body mass index (BMI) which predicts the lowest mortality increases with age and differs by sex. Yi *et al.* make the cognitive leap to interpret this observation as indicating that gaining weight gradually and becoming overweight with age may not be particularly harmful for longevity in individuals with normal weight, especially at older ages and in women.¹

Scientifically we expect causal factors to be consistent over space and time, unless we have reason to think otherwise. Yi *et al.* do not provide any mechanistic explanation for the effect of BMI on mortality varying by age and sex. Increasing optimal BMI with age could be due to selection bias and confounding. Overweight or obese people surviving to older ages might be those most resistant to any adverse effects of adiposity. In a national survey of ages 18 to 99 years, as used by Yi *et al.*, with increasing age recruits are more and more strongly selected healthy survivors from their original birth cohort, giving a biased estimate of the lifetime effect of BMI. Moreover very few adults achieve intentional weight reduction,² so with increasing age the ‘normal’ BMI group are more and more likely to be those who have lost weight because of illness prior to and symptomatic of impending death, which generates confounding unless health status is comprehensively taken into account. In contrast, an overlooked factor that could contribute to higher BMI being less detrimental in men than women does exist. Increasingly, evidence suggests that testosterone is a causal risk factor for a leading cause of death, cardiovascular disease;^{3–5} obesity substantially reduces testosterone in men.⁶ However, whether such a mechanism translates into different effects of obesity in men and women has not been

assessed, and may well not offset the adverse effects of obesity established in studies—such as Mendelian randomization (MR)—better suited to establishing causality from observational data.⁷

Notably, Yi *et al.* do not take their interpretation to its logical conclusion and suggest a randomized controlled trial to test, in generally well-fed populations, whether weight gain at the lower end of the BMI range decreases mortality, which casts further doubt on the interpretation they give. Nevertheless, Yi *et al.*’s paper with its emphasis on a causal interpretation, despite potential biases in the analysis, may detract from public health efforts to combat the obesity epidemic. Risk factors may be interpreted as reliable predictors of disease, useful perhaps for risk stratification, without indicating corresponding causal effects or, in an unbiased analysis, as causes of disease that represent legitimate targets of intervention. The use of different study designs, such as randomized controlled trials, MR or observational studies in suitable settings, to distinguish causes from ambiguously termed ‘risk factors’, would be very helpful in ensuring appropriate interpretation and corresponding action.

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Author's Response to the Letter: Does the optimal BMI really vary by age and sex?, by Xu *et al*.

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In the comments on our study of optimal body mass index (BMI) associated with a minimal mortality according to sex and age,¹ Xu and colleagues noted that underestimation of risk associated with overweight and obesity, due to selective survival with advancing age, is possible.² However, we would like to point out that this could be more the case for those with a BMI below the optimal range than for those with a BMI above the optimal range since, among survivors after early follow-up compared with all participants, relative risks generally decreased in those with the lowest BMI categories, but not in those with the highest BMI categories in our study, regardless of sex and age. Therefore, selective survival bias, if it exists, is more likely to shift the lower end of optimal BMI downward than shift the upper end of optimal BMI upward in each sex-age group in our study population.

Xu and colleagues also note that more research is needed to identify the appropriate approaches for the public and clinicians to take regarding body weight. We agree. As noted in our article, the optimal body weight for height associated with a minimal mortality increases with age and differs by sex in Korean adults.¹ One of the potential mechanisms is height change with age. Height decreases with advancing age, especially in women.^{3,4} Therefore, BMI increases with age independently of weight change, especially at older ages,

particularly in women.^{3,4} Changes in sex hormones with age could also be related to our findings, as suggested by Xu and colleagues.^{2,5–7} Many important issues regarding optimal body weight, including causality and mechanisms, remain unclear. The sex-age-specific optimal range for BMI may vary by ethnic group.⁸ Due to a lack of evidence on the effects of intentional weight change (loss or gain) on overall mortality and major cardiovascular complications, according to sex, age and body weight levels, there is uncertainty about implementing intentional weight loss or gain for better health: for whom, when and how.⁹ These questions should be examined through future research including well-planned randomized trials and observational studies using methods to minimize bias and ensure more definitive answers to causality and mechanism.

Irrespective of arguments around causality, our findings suggest that low-normal weight (such as 18.5–22.9 kg/m²), in addition to underweight and obesity, should not be considered a sign of good health without careful evaluation in men at any age and women aged 50 years and above. Public health efforts to prevent and manage health issues related to body weight—not just obesity, but also underweight and low-normal weight—should be strengthened for better health.

Conflict of interest: None declared.