Challenges in estimating the causal relationship between BMI and mortality

Authors: Dr Kathryn E Bradbury (Senior Research Fellow)[1] and Dr Benjamin J Cairns (Senior Statistical Epidemiologist)[2]

[1]National Institute for Health Innovation, School of Population Health, The University of Auckland, Auckland 1072, New Zealand
[2]MRC Population Health Research Unit, Nuffield Department of Population Health, University of Oxford, Oxford OX3 7LF, United Kingdom

Corresponding author: Kathryn E Bradbury

Email address: k.bradbury@auckland.ac.nz

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High body fatness is an important cause of ill health[1]. Sun and colleagues, in this article in the BMJ [link], use two cohort studies—the Norwegian HUNT study and the UK Biobank—to investigate the relationship between body mass index (BMI) and mortality[2]. BMI—weight (kg) divided by height squared (m)—is often used as a simple proxy for body fatness, because most of the variation in BMI is due to variations in body fatness[3]. Large observational studies consistently report J-shaped associations between BMI and mortality[4-8]. Confounding by smoking and reverse causation (whereby diseases that lead to death may cause weight loss) are important sources of bias in this estimated relationship. These biases shift the apparent optimum BMI upwards and exaggerate the increased mortality at low BMIs. Studies that have attempted to control for them have generally found an optimum BMI around 22-25 kg/m^2 in most populations[4,6-8], but important questions about the BMI-mortality relationship have not been satisfactorily resolved, including:

- Is lower BMI a genuine cause of higher mortality within any part of the normal weight range (18.5-25 kg/m^2)?
- What is the optimum BMI and is it the same in different populations?
- If low BMI is causally associated with higher mortality, is this due to low fat mass, low non-fat mass, or both?

Sun *et al.* use Mendelian randomisation (MR) to try to better estimate the shape of the causal relationship between BMI and mortality[2]. Mendelian randomisation combines a genetic prediction of the exposure (in this case constructed from genetic variants associated with BMI in the GIANT consortium[9]), with an estimate of the genotype-outcome association, to estimate causal effects of the exposure on the outcome. Most MR studies estimate linear effects, but to address the possible J-shape in the BMI-mortality relationship, Sun *et al.* also estimate a non-linear causal effect.

What does this study contribute to the questions posed above? First, the estimated causal relationships between BMI and mortality are J-shaped in both the UK Biobank and HUNT studies; another recent study of UK Biobank, employing similar non-linear MR methods, reported qualitatively similar results[10]. From these analyses, there is evidence of causal associations of lower BMI with higher mortality below about 20-22 kg/m^2. Sun and colleagues additionally present analyses stratified by smoking status, finding little or no J-shape in the association in never smokers, but a more pronounced J-shape in ever smokers. One possibility is that this is driven by respiratory diseases, which are much more common in ever smokers, and that a relatively higher BMI may offer some protection against death from respiratory disease[2,10].

Second, a best guess from Sun and colleagues' analysis is that the BMI with the lowest mortality might be around 24 kg/m^2. Neither the UK Biobank nor the HUNT studies were large enough to estimate this quantity with precision, and these findings cannot yet be generalised to non-European populations. Nonetheless, the results are broadly consistent with the best evidence from the classical epidemiological studies that have tried to limit the effects of smoking and reverse causation.

Third, if low BMI is causally associated with higher mortality, it remains unknown whether low fat mass or low non-fat mass (or both) is driving this. Low non-fat mass has been

suggested to be important in individuals with low BMI[11]. However, genetic variants for BMI commonly affect both fat and non-fat mass[12,13]. Consequently it may be very difficult to disentangle these components of BMI even with approaches such as MR, although attempts are being made to do so[13].

MR studies make several assumptions about genetic variants: that (i) they must be sufficiently strongly associated with the risk factor of interest (BMI); (ii) their associations with the outcome (death) must not be confounded by other factors; and (iii) they may only affect the outcome (death) via the risk factor of interest (BMI)[14]. Potentially the most problematic assumption for Sun *et al*. and other MR studies of BMI is (iii). Smoking behaviours, in particular, may be influenced by and in turn influence BMI throughout life, which complicates interpretation of the main analysis. In the supplement [link], Sun et al. refer to simulation studies which suggest that other potential biases due to stratification by smoking are negligible.

UK Biobank (especially) offers rich opportunities to investigate the relationship between BMI and mortality in more detail, particularly with forthcoming data such as body imaging becoming available at a large scale for the first time[15]. Much more research is likely to come from this UK cohort. But in addition to new data types and new methods, new cohorts in other populations are needed to test the robustness of findings and to understand these fundamental questions about human health at a global scale. For an individual with low BMI, previous literature and the recent MR studies do agree that this can be linked to a higher risk of death, either as a cause or a consequence of disease, and especially in smokers (of course, smokers will best reduce their risk of premature death by quitting smoking). Overall, public health recommendations that people should aim for a BMI within the normal weight range should remain unchanged.

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