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There have been many prospective studies of associations of body-mass index (BMI; weight/height²) with mortality, but some of them have failed to distinguish associations of BMI with mortality shortly after the BMI measurement was made from associations of BMI with mortality several years after it was made. Associations of measured BMI with mortality within just a few years of the BMI measurement can, however, be strongly distorted by reverse causality (ie, by life-threatening neoplastic, respiratory, vascular or other disease having caused weight loss before the BMI was measured). In contrast, associations of measured BMI with mortality several years after the BMI measurement should be little affected by reverse causality, although they can still be strongly affected by confounding, especially in populations where low BMI is correlated with smoking.

To help assess causality (ie, adverse or protective effects on disease rates *caused* by certain determinants or close correlates of BMI), analyses should seek associations of cause-specific mortality with the BMI as it was *before* the onset of any weight-changing disease. So, the Global BMI Mortality Collaboration adopted a uniform statistical approach across all studies and limited the distorting effects of reverse causality by excluding participants known already to have had some serious disease when their BMI was measured, and those dying or lost <5 years after measurement.¹ Also, to limit confounding, the analyses excluded current/former smokers.

The **Figure** shows findings in the remaining never-smokers (1 million men, 3 million women, mainly Europe/North America/East Asia). In these populations, mortality is minimal for BMI 20-25 kg/m², higher for overweight (25-30 kg/m²), and much higher for grade 1 obesity (30-35 kg/m²). Compared with minimal-mortality, the relative risks of 1.7 and 1.4 for men and women with grade 1 obesity suggest, respectively, potential avoidability of ~40% and ~30% of their overall mortality.

The hazards associated with low BMI (15-18.5 kg/m², a range where the variation in BMI mainly reflects variation in factors other than adiposity) were comparable with those associated with grade 1 obesity, suggesting that some important correlate(s) of underweight can also cause disease. The importantly different BMI-mortality relationships in different BMI ranges could suggest importantly different relationships in populations with different major determinants of BMI, and perhaps different major causes of death. (Our collaboration had no data on African populations, and only limited data on South Asian populations.)

In the UK Million Women Study (the largest single contributor to this collaboration), self-reported and measured BMI differed on average by only 3%, with 95% correlation between them.² Hence, as self-reported BMI is such a close correlate of measured BMI, there is no need to fear³ any material uncertainty in the relative risks from the use of self-reported BMI values.

It is well-recognised that relationships of BMI to subsequent disease rates in the general population may be very different⁴ from the various relationships of BMI to prognosis among patients who already have particular diseases. To help assess the causal relevance of the ordinary correlate(s) of BMI to disease onset in the general population, the Collaboration's main analyses were therefore restricted to BMI measurements in general populations without pre-existing disease.

The cited^{5,6} meta-analysis of the joint relevance of BMI and cardio-respiratory fitness to mortality is based chiefly on North Americans attending one particular fitness program, among whom the main determinants of BMI may well have differed substantially from the ordinary correlates of BMI in the general population. Further investigations in large studies of populations much less stringently selected than those attending US fitness clinics (eg, UK Biobank⁷) are therefore needed before hypothesising that stratification for cardio-respiratory fitness might transform the BMI-mortality relationship in the general population.

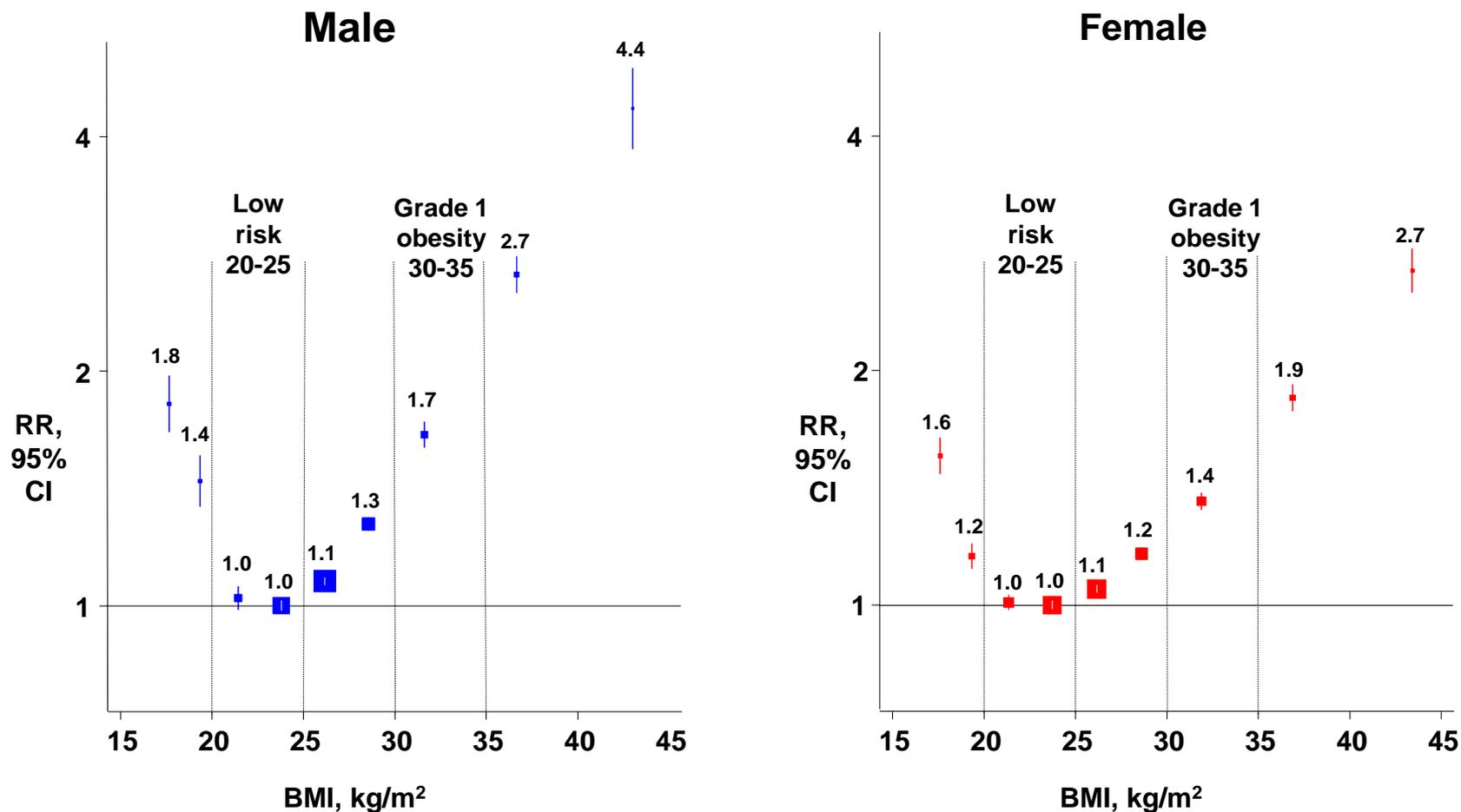
Emanuele Di Angelantonio, Shilpa N Bhupathiraju, Frank B Hu, John Danesh, Richard Peto, Sarah Lewington for the Global BMI Mortality Collaboration

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Figure

Association of body-mass index (BMI) with all-cause death rate ratio (RR)



Analyses are restricted to never-smokers without pre-existing chronic disease who survived >5 years after BMI was measured. For each group, square size is proportional to the variance of the log risk in that group and the 95% CI reflects only this variance.