Fundamental limitations of meta-analysis of cohort studies, epidemiological challenges and the stage of obesity epidemic.

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Meta-analysis can generate useful results but can be controversial or confusing. Flegal's meta-analysis showed over-weight did not increase mortality risk[1] but a much larger meta-analysis found over-weight did increase risk when the analysis was restricted to nonsmokers at baseline.[2] Both were based on baseline BMI and did not account for health and obesity status before and after baseline. But both showed clearly that obesity kills. World Health Organization advocates for healthy diet and physical activity to halt the rise of global obesity, but weight reduction is not highlighted.[3]

Karahalios and colleagues'meta-analysisis the first to show that weight loss and weight gain in midlife are associated with increased risk of all-cause and cardiovascular disease mortality, and weakly associated with cancer mortality.[4] They discussed weight loss intention, effect modification, reverse causation, bias and confounding, and stated that "this is the highest level of evidence possible" and "these observational data suggest weight stability from middle age, however, further research investigating effect modification by obesity status is warranted."[4]

Although the authors did not recommend weight stability regardless of health and weight status, the results based on observational data could be easily misinterpreted with adverse public health implications. Our interpretation is that their result that weight gain showed higher risk than weight stability is plausible and can confirm that increased adiposity is harmful. Such increased risk can be more easily observed when obesity has been rapidly increasing globally during the follow up period of the cohorts, and we would expect more unhealthy weight gain and related harms than healthy weight reduction and related benefits in many cohort studies. However, the result that higher risk for weight reduction is unexpected and more problematic, which is most likely due to reverse causation, as the adverse effects of unintentional weight loss due to ill health and aging in many subjects would overwhelm the benefits of intentional weight loss in the few.

The fundamental limitation of meta-analysis of observational studies is the lack of data on lifestyle, health, adiposity, intervention and weight loss intention in the life-course before baseline and during follow-up. These factors may add to, counteract, or overwhelm the effects of weight changes.

For cohort studies, the first challenge is to assess weight fluctuation (i.e., weight loss after weight gain, or weight gain after weight loss) at multiple time points. Reliable and affordable methods for long-term monitoring of weight trajectory are needed. The second challenge is to determine the reasons and methods by which weight change is achieved in people with different weight trajectory, health and disease status, and lifestyle changes (such as stopping smoking) and effects of treatment. The third challenge is to go beyond BMI and collect data for other indicators of adiposity, and biomarkers using new technologies. The fourth is aging, which typically leads to loss of lean body mass and muscle strength, and increase in fat mass. Statistical adjustment for age will mask effect modification. The assessment of effect modification needs to consider the age range of the subjects included, insufficient statistical power, and length of follow up (a long follow up is needed for younger subjects for mortality). The results from a failure to observe significant effect modification by age does not mean that the results can be generalised to all people at middle age or other ages. The same applies to no significant interaction by baseline weight status or weight reduction intention, and the results cannot be generalised to all people regardless of the above variations.

Given the many difficulties in observation studies, Mendelian randomization (MR) using genetic variants that predict individuals who are more prone to weight gain or weight loss as instrumental variables can provide analogous evidence to randomised controlled trials (RCTs). MR has been increasingly used to clarify causal relationships from observational studies and to prioritise potential targets for intervention.[5] But evidence on the effects of weight changes from

intervention studies, especially from RCTs, is still urgently needed. RCTs on weight reduction in people with under- or normal weight, and on weight increase in people with normal or overweight are unethical. RCTs on weight reduction interventions on those who are overweight or obese can evaluate the cost effectiveness of different interventions on different target groups. The effects of weight stability can be assessed within RCTs by comparing those with weight changes (increase or decrease) with those with no change.

More importantly, meta-analyses on the effects of a risk (or protective) factor at baseline or the change of a risk factor from baseline to follow up, need to be interpreted in relation to evidence from intervention studies to reduce (or increase) exposure to the risk factor. A 2015 meta-analysis of RCTs showed a 15% lower all-causal mortality risk with an average weight loss of 5.5 kg in those with mean BMI of 30-46 kg/m^2.[6] As meta-analyses on RCTs can provide much stronger evidence than meta-analyses on observational studies, we recommend that the RCT evidence, and weight reduction interventions, should be highlighted in future WHO fact sheets.

The most important and never ending challenge is that the obesity epidemic is still at the early stage as obesity prevalence is increasing. The 'stage of epidemic' model was first used for tobacco, which shows a gap of a few decades between the peak of smoking prevalence and the peak of percentage of death attributable to tobacco.[7] Cohort studies on smoking set up more recently or with subjects born more recently showed higher risks than cohorts set up or subjects born earlier (in the US and UK: relative risk for all-cause mortality has increased from 2 to 3).[8] The benefits of mortality risk reduction from quitting, based on follow up data of stopping smoking in smokers at baseline, can only become clear after a few decades of follow up. As obesity prevalence started to rise several decades later than smoking prevalence, more adverse effects of obesity will emerge from more recent research. Because of the long latent period and the cumulative effects of obesity over time (obesity starting at infancy and childhood, rate of

increase, and severity and duration of obesity), past cohort studies on overweight and obesity would yield under-estimated risks.

While ill health will always be a major cause of weight loss, with increasing obesity control measures, healthy weight loss would increase, and has been observed, such as in Hong Kong[9] and Guangzhou[10] China. Such changes, reasons for the changes and subsequent health benefits should be monitored and analysed. Moreover, the benefits may vary by the magnitude of change, the lifetime trajectory of weight status, the age at which weight loss started and duration of persistent weight loss. Hence, large biobank cohort studies (0.5 to 1 million subjects, including younger subjects) need to be set up periodically (every 10 years) in countries at different stages of the obesity epidemic, with data and biomaterial collection at baseline (including past health related data) and follow up (including reasons/methods of weight change) using more standardized methods, to allow for individual participant data meta-analyses. A large international collaboration is urgently needed. Otherwise, epidemiology in general, or cohort studies in particular, will always lag behind the evolution of the obesity epidemic.

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