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Estimating chronic disease risks related to adiposity in two German prospective cohorts

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A plethora of epidemiological studies have shown that obesity is a substantial risk factor for the development of chronic diseases, such as type 2 diabetes mellitus (T2D), cardiovascular diseases and several forms of cancer, such as colorectal cancer (CRC), breast cancer in postmenopausal women, and endometrial cancer. Obesity is mostly assessed by anthropometric indices, such as body mass index (BMI) and waist circumference, which are surrogate measures of overall body and abdominal fat. The use of those surrogate measures leads to an imprecision in measurements of body fat and lean tissue compartments, and is likely to result in misclassification of individuals with respect to the volumes of total body fat, visceral fat, subcutaneous fat, but also muscle tissue. As to a large extent this misclassification may be random, it will likely lead to an underestimation of relative risks of disease in relation to body composition.

To assess the possible magnitude of such an underestimation, a large-scale validation study (N=1,192) using magnetic resonance imaging (MRI) as the gold standard method was conducted within the European Prospective Investigation into Cancer and Nutrition (EPIC)-Germany. Within this sub-study, it could be seen, that especially the internal body fat compartments (visceral and coronary adipose tissue) as well as skeletal muscle tissue were poorly predicted by anthropometric indices. In order to increase the prediction capacity, the use of additional blood-based biomarkers was investigated on participants of the sub-study. This approach showed only fair increases in the prediction capacity of visceral adipose tissue (R^2=4.0% in men, R^2=4.8% in women) despite extensive literature research on possible biomarkers related to visceral fat and a sub-sequent large amount of measured biomarkers. In a following step, it was therefore investigated whether the use of bioelectrical impedance analysis (BIA) measures of total body fat and muscle mass may increase the prediction of body compartments. Here, the results showed that the prediction of muscle mass may be increased by the use of BIA measurements by ~20% in men, and ~15% in women, however, the prediction capacity of visceral fat still remained limited (increase in R^2 of ~2%). As these two approaches (blood-based biomarkers and BIA measures) did not yield significant increases in the prediction capacity of visceral fat, the magnitude of underestimation was calculated based on anthropometric indices, only.

Results showed that the use of BMI and waist circumference as surrogate measures for total and visceral fat led to a considerable underestimation of attributable risks (AR) for chronic diseases, namely T2D, MI, stroke and CRC, of 31% (95% CI: 23%; 40%) in men, and 40% (95% CI: 31%; 49%) in women. When applying the BMI threshold of $\geq$ 25 kg/m², and the corresponding waist circumference (90.1 cm) in men, an additional 4,754 cases (13%) of the

reported CRC cases in Germany in 2012 may be attributed to high abdominal and general body fat, but are not captured as such when using the surrogate measures BMI and waist circumference.

Given that measurement errors and misclassification may also occur from single measurement assessment, the present work also investigated whether weight variations over time, especially weight cycling may affect visceral adiposity, and disease risk. Thus, it was investigated, whether sub-study participants with different weight patterns had different levels of visceral fat. It could be seen that weight cycling (weight loss followed by weight re-gain or vice versa) was not associated with substantially higher levels of visceral fat in the sub-study, and that within the sub-study the highest amounts of visceral fat were found in the weight gain category. Weight patterns were further investigated in relation to T2D risk using two different approaches, and results showed that while *a priori* defined weight cycling was associated with increased T2D risk, *a posteriori* defined weight cycling by functional principal component analysis was not. The findings therefore suggest that, unlike obesity, followed by overweight and weight gain, weight cycling may not be a strong independent risk factor for T2D in adults. Particularly weight cyclers, who maintain net weight stability, may not be at a higher risk of diabetes compared to non-cyclers. However, the observation of a potentially increased diabetes risk related to weight cycling *during* weight gain clearly requires a cautious interpretation, until confirmed by other studies.

Overall, the present results underline that weight variation over time, which is often not considered in epidemiological studies, affects diabetes risk. However, weight status and weight change seem to play a more important role than weight cycling. Even if one considers that weight loss is more often achievable than long-term weight maintenance, results indicate that the risk of weight regain may not outweigh the benefits related to successful weight loss. It could also be demonstrated, that the risk attributable to total and visceral fat, is most likely to be even higher than that reported in previous studies using anthropometric indices as surrogates for regional and overall body fat, and underlining the relevance of this topic. It is therefore highly recommended to conduct sub-studies within well-defined cohort studies to assess the degree of underestimation of disease risks. For future cohort studies, the use of BIA measures in addition to anthropometry is a valuable asset in conducting research on body compartments and related disease risks, especially with regard to a growing number of older people in the population, and therefore a higher risk of sarcopenia and frailty in the future. When considering the high prevalence of obesity and the fact that even with moderate risk estimates of diseases, this prevalence leads to high AR, the magnitude of the prevention potential in the population as well as the importance of the obesity topic in general, become very apparent. Thus for the future, it remains crucial to strive towards better prevention strategies of obesity as this might substantially decrease disease risk.