Body Mass Index in Children Validated by Metabolic and Fat Mass Profiling*

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In this issue of the Journal, Bell et al. (1) report longitudinal findings on the interactions between adolescent fatness and cardiometabolic risk factors and the quality of the body mass index (BMI) as the established screening tool for fatness. This area of research is important for several reasons. First, the foundations of a healthy life are set in youth, but up-to-date trajectories of cardiometabolic traits are often uncertain in underage population segments because of lack of data, which makes it harder to develop evidence-based interventions and health criteria. It can also be argued whether prevention programs against cardiovascular disease decades beforehand make sense; a complete longitudinal picture of the molecular etiology of cardiometabolic dysfunction would clarify matters. Second, obesity in youth predicts cardiometabolic dysfunction in adulthood (2). Unfortunately, we as a society—families, educators, community leaders, and others alike—are failing to curb rates of childhood obesity (Figure 1). What will happen in the next 50 years when the sedentary and overweight children graduate to diabetes and vascular complications?

Third, weight loss and changes in behavior are hard to achieve in an obesogenic environment, but maybe the metabolic stress from obesity can be mitigated with the help of high-fidelity metabolic data such as those collected by Bell et al. (1). Even the “fat but fit” may eventually convert to metabolic dysfunction given enough exposure (reviewed by Jung et al. [3]). Therefore, accurate measurements of the complex relationships between body mass, fat gain or loss, and changes in circulating metabolites across all age groups (including children) are warranted to monitor the situation and to develop effective ways to turn the tide.

Weight gain does not happen overnight, so longitudinal study designs with sufficient follow-up are the preferred source of evidence. Although it is tempting to draw conclusions by comparing young and old or lean and fat cross-sectionally, such study designs are confounded by differences between age groups and other contextual factors. In this respect, the dataset from ALSPAC (Avon Longitudinal Study of Parents and Children) that Bell et al. (1) used is rare and valuable, as they have prospective data over several years, and the study subjects were children at the time. The study also benefited from sophisticated body scanning technology that allowed them to separate the main areas of fat in the body. This is important, as previous studies suggest that the location of fat makes a difference (4), colloquially expressed often as “male obesity is apple shaped and female obesity pear shaped.” Indeed, Bell et al. highlight abdominal fatness as a primary driver of cardiometabolic dysfunction, whereas leg fat appeared to be less dangerous. But BMI does not work well in detecting the distribution of fat, and it might not capture the metabolic sequelae of fatness, which has led to criticism against its widespread use (5).

Bell et al. (1) observed that changes in BMI and fat mass index within the second decade of life were both associated with circulating cardiometabolic risk factors in the late teens. They conclude that “fat gain is not beneficial in any region.” This take-home message is important, because it solidifies fatness as the key modifiable factor to maintain healthy

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metabolism in young people. The good news is that a single BMI measurement may be enough to capture the same essential information as a detailed body scan and serial measurements. Consequently, BMI remains a highly useful and cost-effective population health tool.

The investigators did not explain the associations between BMI and other risk factors by physical activity, as there is evidence that obesity affects activity rather than vice versa (6) and that weight loss by increased activity alone is difficult (7). Nevertheless, a persistently active lifestyle is associated with a beneficial metabolic profile (8), and it is reasonable to expect that most lifestyle factors are causally interlinked to some degree within a broader sphere of well-being. Therefore, the conclusions by Bell et al. (1) should not be interpreted as arguments against the importance of exercise in maintaining physical and mental health.

The investigators relied on nuclear magnetic resonance (NMR) metabolomics profiling to investigate the molecular aspects of fat distribution and changes in fatness. This platform is an emerging metabolic screening tool with excellent reproducibility and a growing catalog of epidemiological applications (9). The study by Bell et al. (1) benefits from the extensive array of lipid and lipoprotein measures that can be captured by the NMR technology. For example, the causal role of circulating cholesterol is well established in the development of atherosclerotic plaque, and the NMR platform provides detailed data on low-density lipoprotein subclasses that are critical mediators of cholesterol accumulation into the arterial wall. In contrast, metabolomics in this context should not be viewed as a tool to discover new biomarkers. The coverage of the NMR method is limited beyond lipids and a few abundant circulating metabolites, and its main strength is providing a general snapshot of metabolic health rather than an exhaustive battery of exotic molecular traits within the traditional remit of metabolomics. Specifically, the investigators replicated longitudinally previous cross-sectional associations between imbalance of very low density lipoprotein and high-density lipoprotein and obesity (10), with consistent accompanying perturbations in blood pressure control and glycemic and inflammatory traits. The contributions of Bell et al. and others demonstrate the usefulness of the NMR platform to detect the cardiometabolic signatures of obesity within human populations.

With new data come new statistical challenges. The paper by Bell et al. (1) draws from a long tradition of linear modeling in epidemiology. This tradition has its roots in an era with very limited computational power and low-dimensional datasets. However, big biomedical data have transformed the methodological landscape, and I would argue that new thinking could enable better communication of findings.
between scientific silos. This does not mean that established methods should be abandoned, but perhaps, new types of analyses that leverage data mining, machine learning, and advanced visualization, or networks of interactions would provide additional insight into the data patterns.

From a population health perspective, excess weight promotes cardiometabolic dysfunction that can be detected already at a young age both cross-sectionally and longitudinally; evidence from cohorts such as ALSPAC is difficult to ignore. At an individual level, one could argue that there is variation (e.g., the fitness vs. fatness debate), but again, the evidence suggests that lean mass has only a minor impact and that fitness measures may reflect mediating rather than causal processes. How fatness is measured may not be that important provided that the major trunk depots are captured, so BMI remains a useful tool in large-scale studies despite its apparent simplicity.

Given the results, what is the broader take-home message to society? The longitudinal metabolic profiling showed that high BMI in children indicates exposure to an adverse metabolic milieu that we know predicts cardiovascular disease later in life. Therefore, childhood obesity must not be seen as a phase that passes but as a looming public health crisis that needs to be addressed by all of us.

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