Editorial

Weight or metabolism: which deserve more attention in obesity?

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Obesity has become an important public health issue worldwide. A previous study has indicated that age-standardized average body mass index (BMI) increased from 21.7 kg/m^2 in 1975 to 24.2 kg/m^2 in 2014 in men, and from 22.1 to 24.4 kg/m^2 in women worldwide (1). With regard to children, it has been demonstrated that the global age-standardized prevalence of obesity increased from 0.7% in 1975 to 5.6% in 2016 in girls (5–19 years old), and from 0.9% to 7.8% in boys (5–19 years old) (2). However, few studies have focused on the prevalence of obesity in children under 5 years old and the incremental acceleration in annual BMI in children and adolescents. One of the major strengths of the study being referenced in this editorial was the population-based design with a large cohort encompassing more than 51,000 children across the entire age span from infancy to adolescence. The results from this study show that obesity occurred early in life (3 years of age) and once present, obesity persisted into adolescence in almost 90%. Furthermore, it has been suggested that among obese adolescents, the most rapid weight gain occurs between 2–6 years of age, indicating that BMI acceleration in this period may be useful in predicting obesity during adolescence. These results provided reliable evidences for the epidemiology of childhood obesity, and give new insight into the prevention of obesity in adolescents and adults as well.

Clinicians and researchers hold two points of view on obesity. The mainstream opinion considers obesity a disease. Previous studies have demonstrated that obesity as defined by BMI is related to increased all-cause mortality in the adult population among all racial and ethnic groups (3-6). More recently, Bhaskaran *et al.* further examined the relationship between BMI and an extensive range of cause-specific mortality outcomes (7). They have found that BMI had J-shaped associations with all-cause, non-communicable, and communicable disease mortality, with the nadir for all-cause mortality risk at a BMI of 25 kg/m^2 among non-smokers.

An alternative point of view is that obesity alone is not responsible for the development of various medical morbidities (8-11). This viewpoint further suggests that BMI should not be the exclusive indicator used for estimating mortality among the obese population. There are three main reasons for this perspective. Firstly, the causes and mechanisms of obesity are multitudinous. A previous study identified at least 77 loci which have been related to obesity (12). Furthermore, 40–70% of inter-individual BMI variation has been traced back to genetic factors (13,14). Moreover, the largest genome-wide association studies (GWAS) meta-analysis for BMI identified 97 genome-wide significant (GWS) loci related to BMI, including 56 novel loci (15). The other common instance is that the increasing levels of BMI and fat mass in post-menopause women (16) are result from senility (17) and the decreased level of sex hormone (18). Secondly, the impacts of obesity on different individuals is not identical (8,9). Individuals having high levels of body adiposity who exhibit a cardioprotective phenotype and have a normal metabolic profile are often

referred to as the "metabolically healthy obese (MHO)" (19,20). Primeau *et al.* have reported that individuals who are MHO account for as much as 18% to 44% of the adults' population (19). Among children, the prevalence of MHO ranges from 4.2% to 68% (21). In addition to this, overweight or obese individuals with impaired metabolic health are defined as the "metabolically unhealthy obesity (MUO)" (22). The increased mortality among the obese population may predominantly be accounted for by MUO individuals. Susceptibility to metabolic or cardiopulmonary dysfunction due to obesity is therefore not mediated by fat content alone, but is dependent on the adipose tissue distribution and the ability of adipose tissue depots to expand (8). Regulation of gene expression, together with epigenetic control of energy balance, determines the status of adiposity of an individual from an early age to later life (8). Thirdly, a concept exists referred to as the 'obesity paradox', which is defined as obesity being protective against mortality in individuals with cardiovascular disease (CVD). Numerous studies have shown that normal weight individuals with CVD have worse survival than do overweight and mildly obesity with the same degree of CVD (10). A study by Flegal *et al.*, found that relative to normal weight, individual with BMI of 30 to <35 (grade 1 obesity) was associated with lower mortality, and individual with BMI of 25 to <30 (overweight) was associated with significantly lower all-cause mortality. This suggests that higher BMI levels may be responsible for driving the increasing mortality among the obese population (23). Indeed, an increasing number of studies have demonstrated the beneficial effects of subcutaneous adipose tissue on metabolism (24). Leptin (25), which is closely related to appetite and glucose metabolism, as well as adiponectin (26), which protects against diabetes, are secreted from subcutaneous fat. More recently, Li *et al.* have reported that the effect of fibroblast growth factor 21 in enhancing insulin sensitivity depending on specific expansibility of subcutaneous fat (27). Overall, clinicians and researchers therefore should pay attention to overall metabolic status and the cause of obesity rather than BMI alone. Interventions should be focused on fitness-based interventions and physical activity rather than treating all obese individuals with weight-loss driven approaches which may be counterproductive. Further research is needed to explore the MHO phenotype during childhood and to investigate its relationship to the overall metabolic status of patients with pediatric obesity.

With regard to obesity prevention, the paper being referenced in this editorial posited that an excessive weight gain during the interval of 2–6 years of age should be regarded as a crucial period for the prediction of obesity in adolescence. This same age period has also been described as an early sign of ensuing overweight in adulthood (28). These results provided evidence that clinicians should pay more attention to the management of weight gain in patients in this age range. As mentioned earlier, metabolic health should also be considered an important indicator for the assessment of obesity. A recent study, by Cirulli *et al.*, introduced a more accurate approach of categorizing and phenotyping risk of obesity rather than using BMI alone (29). Cirulli *et al.* used non-targeted metabolomics and whole-genome sequencing to confirm metabolic and genetic signatures of obesity and found that the metabolome captures clinically relevant phenotypes of obesity. They identified 49 metabolites that were associated with BMI, including lipids, amino acids, nucleotides, and peptides, among others. Urate was most significantly associated with BMI among the 49 metabolites. Thereafter, they used ridge regression as well as lasso regression to establish a BMI prediction model which was defined as mBMI on the basis of the metabolome. This model based on the 49 BMI-associated metabolites, as well as age and gender explained 43% of the variation in BMI. In predicting whether participants were obese or normal weight, the model had an area under the curve of 0.922 with 89.1% specificity and 80.2% sensitivity. They found that at any given BMI, abnormal metabolomes were associated with different health outcomes; those whose mBMI was greater than their actual BMI were marginally more likely to gain weight and convert to an obese phenotype over the 8–18 years of follow up; and those with healthier metabolomes to have fewer cardiac events. These results are consistent with a favorable long-term health benefit for overweight and obese individuals with a healthy metabolome, and also suggested that the mBMI can be used as a clinically meaningful metric.

In conclusion, the current trend in obesity management is to combine BMI with metabolic health to categorize obesity and estimate the degree of severity of obesity in children, adolescents, and adults. In addition, more population-based studies that combine of both BMI and metabolic health are needed to explore the all-cause mortality and specific cause mortality in obesity.

This article is worth reading for all providers taking care of patients with obesity, as it provides information for the first time regarding the epidemiology of obesity in children under 5 years old. Additionally, this study gives new insight

into the value of the BMI acceleration in the period of 2–6 years in predicting obesity in adolescents. We believe this study will give clinicians valuable information to guide their practice treating young children with obesity.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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