BMI trajectories from childhood: The slippery slope to adult obesity and cardiovascular disease.

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The increased prevalence of obesity during the past three decades has alarmed the global health community. Four million deaths and 120 million disability-adjusted life years worldwide are related to excess body weight and although the trend appears to have stabilized in some developed countries, the problem is spreading in the developing world[1]. If recent trends continue, it has been projected that 60% of the world's population could be overweight or obese by 2030[2].

The causes and consequences of obesity are complex[3]. A combination of inherited genes that confer susceptibility and an environment that is increasingly characterized by a sedentary lifestyle and consumption of excess calories are thought to be the main predisposing factors. Adipose tissue produces hormones such as leptin and adiponectin, chemical messengers and cytokines that may affect the development of cardiovascular disease (CVD)[4]. A number of studies have consistently demonstrated a strong association between obesity, especially visceral adiposity, and insulin resistance, which is the main contributing factor for the development of type 2 diabetes (T2DM), hypertension and CVD.

The most rapid rise in overweight/obesity has occurred in the young and the majority of overweight/obese children will unfortunately become obese adults[5]. This will add to the population of adults who have become obese by accumulating fat in later years and will have major global public health and economic consequences. Elevated BMI has been associated with adverse cardiometabolic traits in both childhood and adulthood and data from numerous longitudinal studies, including the Fels Longitudinal Study, the Bogalusa Heart Study and the Young Finns Study demonstrate that BMI tracks from childhood to adulthood[6].

As the global health community is focusing on developing and establishing treatments and prevention policies to address obesity, more information about the influence of increased BMI at different periods of life (from childhood to adulthood) and its impact on specific cardiometabolic traits as well as overt CVD is needed. The recent study by Busco MJ and colleagues, from the Young Finns Study, provides novel information on this topic[7]. By using lifecourse analysis, the authors uncover the effects of BMI trajectories from childhood on later cardiovascular outcomes. This type of analysis, avoids the limitations of discrete categorization and classification

and can identify heterogenous patterns of individual behaviour. Six distinct trajectories were described to characterize patterns of adiposity progression in their cohort. Consistent with previous reports, trajectories of worsening or persisting obesity, which translate to longer adiposity exposure, were common and were associated with increased risk of adverse CV outcomes in adulthood (such as dyslipidemia, hypertension and risk for T2DM). The higher the BMI trajectory grade, the higher the probability of having at least one elevated CVD risk factor in adulthood. This supports the consensus that exposure to excess BMI years increases both T2DM and CVD risk factor levels. Increased subclinical atherosclerosis as quantified by carotid intima media thickness (cIMT) was also noted with increased adiposity exposure.

BMI was used to describe adiposity status as it is strongly associated with total body fat content in adults and correlates with other adiposity measures in both children and adults[8]. Its use, however, across the lifecourse is more problematic as it does not consider body fat distribution and cannot discriminate between fat mass and lean mass. Rapid changes in body composition occur, especially in adolescence, with increase in fat mass in girls and muscle mass in boys. Waist circumference may be a better marker of central adiposity but it is prone to measurement error. Global and regional fat distribution can be more accurately assessed by dual-energy X-ray absorptiometry (DXA), computed tomography (CT) and magnetic resonance imaging (MRI) but these are not easily applied to large cohorts. Further detailed studies of fat and vascular phenotype in selected subgroups of the Young Finns population would be invaluable.

Busco and colleagues make further interesting observations on the relationships between BMI trajectories and the different cardiovascular risk factors and type 2 diabetes in later life[7]. The pattern and impact of association between adiposity trajectories and cardiometabolic traits was not consistent.

The absence of BMI stabilization in adulthood was a stronger determinant of adult T2DM risk than the age at which obesity developed. These data complement previous reports that demonstrate that risk of T2DM is mostly associated with increased BMI close to the time of diagnosis[9]. They also support findings from the

Whitehall II study, in which lifecourse analysis identified that patterns of obesity development were accompanied by different trajectories of insulin resistance and other cardiometabolic risk factors[10]. It is therefore likely that the degree of beta cell failure, the key determinant for T2DM development, differs by BMI trajectory and this should be considered when calculating the risk for T2DM in overweight and obese individuals [10]. As far as diabetes prevention is concerned, it might be optimal to focus on promoting weight loss in adulthood and preventing weight gain during lifecourse rather than focusing on timing of obesity development.

For dyslipidaemia and especially hypertension, the pattern of association with BMI trajectories was different, so that reduced lifecourse adiposity exposure was associated with lower risk of hypertension in adulthood[7]. This finding is also consistent with previous reports, which demonstrate that childhood adiposity, weight gain from childhood to adulthood and adulthood obesity are strong determinants of adulthood hypertension[11]. The pathophysiology of obesity related hypertension is multifactorial. Sympathetic nervous system stimulation in response to increased insulin and leptin, activation of renin-angiotensin-aldosterone system, decrease in natriuretic peptides and changes in salt sensitivity and balance can all occur with increasing levels of visceral adiposity in childhood and adulthood[12]. Therefore, maintaining stable weight gain or losing weight at any period in lifetime is beneficial for blood pressure control during lifespan[13, 14].

The potential impact of patterns of BMI, including normalization, on later cIMT measurements has been explored. The information should be interpreted with caution as only <2% of the study population had a "resolving" pattern of BMI. Consistent with previous reports, the authors have demonstrated that the longer the exposure to adiposity the higher the cIMT in adulthood[14, 15]. Normalisation of BMI in adulthood, however, did not impact on cIMT. It is therefore possible that targeting obesity in adulthood might be too late for atherosclerosis disease prevention, as arterial changes may be established and irreversible. It should be noted that cIMT in the young may be related both to lean and fat mass and may therefore not be as good a marker of atherosclerosis as in adult populations.

Interventions at an earlier phase to modify BMI trajectories may be necessary in order to reduce later atherosclerotic risk. Although the findings of the current report contradict those from other cohorts, which demonstrate minimal influence of childhood obesity on arterial pathology in the young[13, 14], they support the general consensus that the earlier the CV prevention is started, the better. Environmental, socioeconomic and lifestyle influences can have different impact on the severity and duration of obesity and its associations with CV risk factors and arterial disease in different populations, and these differences possibly explain the inconsistencies in the published results. Nevertheless, early CV prevention is important, as there is enough evidence to suggest that, even if high levels of risk factors are successfully controlled later in life, considerable morbidity remains.

Prevention and treatment of obesity ultimately involves adapting a "healthy lifestyle attitude" with increased physical activity and reduced high fat energy intake. Lifestyle interventions to target obesity are essential, but without change in attitude, these can only provide modest results in both adults and children. Disappointingly, rapid re-accumulation of adiposity after the end of intervention has been consistently demonstrated. Pharmacological and surgical interventions provide more sustainable results but have complications and are unlikely to be the standard of care to target overweight/obesity in childhood. Weight loss is important and should be encouraged at any stage in life to reduce CVD risk. As early life factors can be crucial in setting up lifelong BMI trajectories, screening programs and initiatives to tackle obesity should start in the young. Children, however, are intellectually and psychologically immature compared with adults and more susceptible to peer pressures. Success in targeting obesity is, therefore, unlikely to be achieved simply by educating children. Improved public awareness, together with initiatives to educate both families and primary care physicians about the link between BMI trajectories and long term CV risk, are a priority.

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Figure title: **BMI trajectory and cardiovascular risk factors.**

Increased exposure to elevated body mass index (BMI) from childhood to adulthood is associated with increased risk for type 2 diabetes, hypertension, dyslipidemia and carotid intima media thickness (cIMT) in adulthood. Losing weight at any time during lifecourse (small arrows), it reduces adiposity exposure (pink dotted line) and has a positive impact on blood pressure and dyslipidemia in adulthood. Reducing or normalizing BMI in adulthood (big arrow) is likely to have more of an impact for type 2 diabetes prevention whereas effective atherosclerotic disease prevention as assessed by surrogate markers (carotid intima media thickness cIMT) will require preventative strategies to start early in life from childhood.