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Lessons Learned and Unanswered Questions about Weight Changes Throughout the Life Course and Cardiovascular Disease

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Most babies start life at a normal (appropriate for gestational age) weight, but most adults are overweight or obese. Of course, what happens in between varies widely, with some babies gaining rapidly to become obese toddlers, some individuals maintaining healthy weight through older adulthood, and all combinations in between. Obesity during childhood, once rare, has increased dramatically (and proportionally more than in adults) over the past few decades. As of 2011–2014, prevalences reached 17% for obesity (95th percentile sex-specific body mass index [BMI]-for-age) and 5.8% for extreme obesity (120% of the 95th-percentile BMI) among youth ages 2 to 19 years, with notable disparities by race, ethnicity, and socioeconomic status.¹

Although obesity is a well-established risk factor for cardiovascular disease (CVD), the implications of timing and tempo of the weight gain are less well-studied. In other words, we know that obesity at a given point is unfavorable, but apart from (potentially) leading to obesity, does the pattern of change in weight or adiposity matter for CVD outcomes? Is it simply BMI in mid-to-late adulthood (when CVD events manifest) that matters?

Alternatively, is it cumulative burden of adiposity, i.e. the area under the curve of BMI (or fat mass) across years of age, that determines CVD outcomes? Or are specific trajectories of weight gain, i.e. early versus late, or rapid versus slow, especially risky? And what about rising BMI short of obesity – is there a reason to intervene on BMI trajectory itself?

To answer these questions, biological plausibility and empirical observation can be considered. In support of the cumulative burden hypothesis, adipose tissue is known to release adipokines and other substances such as plasminogen activator inhibitor-1 (PAI-1) that promote inflammation, endothelial dysfunction, and atherosclerosis.^{2,3} It is well established that atherosclerosis starts at the beginning of life, so perhaps adipose, the substances it releases, and atherosclerosis are all related in an additive fashion over the life

course. Accordingly, in the Coronary Artery Risk Development in Young Adults (CARDIA) study, cumulative excess BMI and abdominal adiposity across young adulthood were strongly associated with incident CVD, with significantly more discriminative power than non-cumulative (time-varying) measures of BMI and adiposity.⁴

Data suggest that beyond overall burden, particular trajectories of adiposity may disproportionately affect CVD risk. For example, rapid weight gain with similarly rapid expansion of adipocytes may trigger greater release of adipokines that promote inflammation and harmful remodeling of nonadipose tissues.⁵ To this end, in the CARDIA study, more steeply increasing BMI trajectories in young adulthood were associated with adverse left ventricular remodeling (i.e., subclinical heart failure) independent of initial or final BMI, supporting the idea that rate of BMI change informs CVD risk.⁶ Timing is another potentially important factor. It has been hypothesized that increases in adiposity matter most when they occur after puberty is well underway, when fat storage shifts from preferentially subcutaneous to preferentially visceral and ectopic (more metabolically active) locations, as a likely hormone-dependent process.⁷ However, the role of dynamic childhood weight patterns in CVD pathogenesis is even less well-studied than that for adults.

In this issue of *Trends in Cardiovascular Medicine*, Bjerregaard and colleagues attempt to address some of these questions in their review of studies examining the relationship between childhood BMI changes and subsequent risk for CVD.⁸ Despite the relevance of pediatric obesity, this question has been underinvestigated, probably because of the long lag time between exposure and outcome. The authors rightly emphasize that data were scarce, and that available studies were potentially outdated (e.g., 1910–1940s birth cohorts with low obesity prevalence) and limited in scope. In particular, most studies examined BMI at only two points, often many years apart, and adjustment for potential confounders (e.g., socioeconomic status, smoking) was generally lacking. Certainly, to create optimal prevention and treatment strategies, we need more carefully assessed exposures using a broad range of methodology to characterize comprehensive patterns of BMI change (e.g. slope of change, trajectories, cumulative) and regional fat distribution (subcutaneous vs. visceral and ectopic), and we simultaneously need the mechanistic understanding of how these exposures translate to CVD events.

Nevertheless, we can make two practical inferences from the reviewed data. First, we already knew that higher BMI at a single point in childhood is associated with higher risks of CVD events and mortality, but the current review offers some hope in this regard. Achievement of a normal BMI by adulthood mitigated – though it did not abolish – the excess CVD risk.⁸ For example, compared with individuals with persistently normal BMI, individuals with high childhood but normal adult BMI had similar risks of dyslipidemia and hypertension but higher risks of elevated carotid intima-media thickness.⁸ Accordingly, in a well-adjusted analysis from British birth cohorts, the odds ratios for coronary heart disease were highest for persistent overweight (child+adolescence+adult: 6.62 [95% CI, 1.94–22.65]) but moderate and similar for overweight across two points (child+adolescence: 3.43 [0.60–19.64]; adolescence+adult: 3.74 [1.35–10.35]) or only adulthood (3.83 [1.98–7.42]), versus persistently normal weight.⁸ Importantly, normalization of BMI after youth overweight was uncommon in that study. Similarly, a recent analysis from the Bogalusa

Heart Study found that whereas 29% of individuals with a nonobese mean childhood BMI developed obesity by adulthood, just 11% of those with an obese mean childhood BMI had BMI <30 kg/m² in adulthood.⁹ This is not surprising, given the biochemical homeostatic mechanisms that work to maintain obesity once established.¹⁰ In short, achieving normal adult BMI after childhood overweight is very difficult, is substantially better from a CVD risk standpoint than staying overweight, but is not able to fully restore the lower-risk state of normal BMI across the life course.

The second inference is more novel and possibly more actionable, an answer to the last of our originally proposed questions: for non-overweight children with increasing BMI trajectories, is there a reason to intervene on the trajectory itself? The data reviewed suggest the answer is yes. BMI gains were generally associated with CVD outcomes independent of actual BMI level, and in studies that did not adjust for BMI, the use of standard deviation scores (SDS) would potentially bias results toward the null because of the ceiling effect (i.e., very obese individuals would have low SDS gains even for large BMI unit gains, whereas individuals with normal weight would have more SDS “room” to increase).⁸ Furthermore, BMI gains were generally continuously associated with CVD across the range of gains, even for children who did not gain enough to become overweight or obese.⁸ Therefore, we need not wait for children to cross the overweight threshold to be justified in intervening.

In sum, the findings reported by Bjerregaard and colleagues provide new support for the well-established concept of primordial prevention of disease, that is, prevention of risk factor development in the first place. Certainly if children are overweight, we should strive to restore healthy weight and thereby mitigate CVD risk. But we might do better to intervene upon increasing trajectories before overweight status is established. Or better still, we should strive to prevent the increasing trajectory itself, by optimizing prenatal and postnatal environments, eliminating disparities, and equitably preserving cardiovascular health from the beginning of life.

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