# *Projected Cardiovascular Impact of Obesity in Children and Adolescents: Will Obesity Increase the Cardiovascular Risk of Women to That of Men?*

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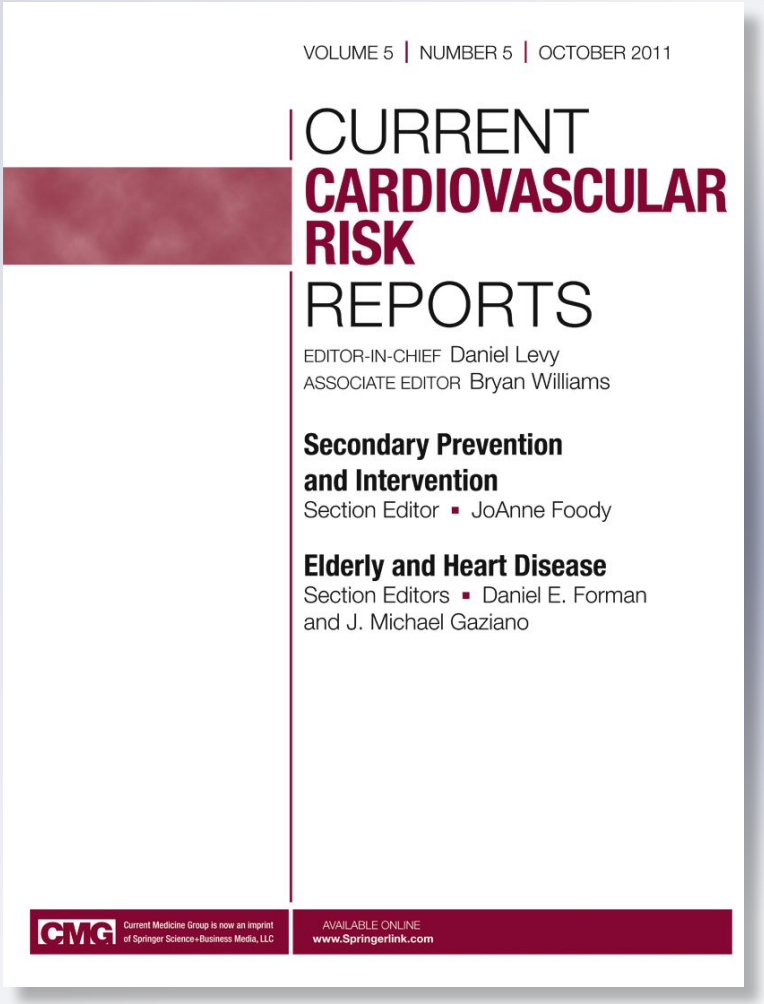


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WOMEN AND CARDIOVASCULAR DISEASE (J ROBISON, SECTION EDITOR)

# Projected Cardiovascular Impact of Obesity in Children and Adolescents: Will Obesity Increase the Cardiovascular Risk of Women to That of Men?

**Jennifer L. Baker · Jens-Christian Holm**



**Abstract** Far too many girls suffer from overweight, obesity, and even severe obesity in childhood and adolescence. The early establishment of excess adiposity is associated with the development of cardiovascular disease (CVD) through complex metabolic aberrations that manifest as components of the metabolic syndrome at young ages. When combined with exposure to other independent CVD risk factors, overweight and obese girls face an elevated risk of cardiovascular morbidity and mortality in adulthood. Additionally, due to their reproductive capacity, women face a different series of risks with regards to the development of CVD compared with men. The risk of CVD accumulates across the lifespan of women, and without a special emphasis in terms of prophylaxis and treatment in younger girls and women, their risk of CVD is likely to equal or even surpass that of men in the future.

**Keywords** Adolescent · Birth weight · Body mass index child · Cardiovascular disease · Coronary heart disease · Morbidity · Mortality · Obesity · Overweight

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## Introduction

Worldwide, levels of childhood and adolescent obesity have reached epidemic proportions. Recently, however, evidence has indicated that there has been a leveling off and even decreases in the prevalence of obesity among children and adolescents from Australia, Europe, and the United States since 1999 [1••, 2]. Evidence from much of the rest of the world, however, is lacking [1••]. Despite the apparent stabilization in many countries, far too many children remain obese and at risk of negative weight-related health consequences, with the future development of cardiovascular disease (CVD) being of particular concern.

In adults, CVD is a leading cause of death worldwide [3]. CVD is, however, largely preventable through the modification of behavioral and metabolic risk factors [3], and only a small fraction of it is attributable to monogenic disorders [4]. Contrary to the perception that CVD is a male disease, women are equally afflicted [3]. The presentation of the disease, its treatment, and prognosis are, however, less favorable in women [3, 5, 6]. In the United States, the 2011 clinical recommendations for preventing CVD in women highlighted the deleterious effects of obesity on CVD risk [7]. Given that far too many young girls are already overweight, obese, and even severely obese, it leads to the question of how this will affect their future cardiovascular health. Therefore, this article explores if the obesity epidemic among girls and adolescents will increase their burden of CVD to equal that of men in the future.

## Early Origins of Childhood Obesity and Cardiovascular Risk

The obese phenotype is extraordinarily complex in nature and is subject to influences from a large variety of exposures

operating in the pre-conception period, during fetal development, and in post-natal life. The developmental origins of health and disease hypothesis states that many non-communicable diseases in adulthood arise from aberrant fetal growth [8]. In response to an adverse intrauterine environment, the fetus makes changes that increase its chances of survival and the plasticity of this response likely continues after birth [9]. Although these adaptations are advantageous in the short-term because they improve survival of the newborn, they may carry long-term risks.

Size at birth is associated with CVD. A recent meta-analysis showed that birth weight was inversely associated with CVD mortality in women [10]. In studies that have closely investigated the shape of the association across a broad range of birth weights, non-linearity in its associations with coronary artery disease in women [11], coronary heart disease (CHD) morbidity and mortality [12, 13], and circulatory disease mortality [14] have been found. Additionally, low birth weight is inversely associated with stroke in adulthood among women [15]. Interestingly, low birth weight in the offspring is also associated with an increased CVD risk in the mothers [16] suggesting that the metabolic processes of pregnancy in the mother that result in small-for-gestational age babies are accompanied by a metabolic phenotype that predisposes to CVD.

Size at birth also has associations with many CVD risk factors such as obesity, type 2 diabetes mellitus (T2DM), and systolic blood pressure (SBP). Birth weight is positively associated with childhood overweight and obesity [17]. Further, women born large-for-gestational age had a significantly increased odds of being obese as an adult [18•]. In general, birth weight is inversely associated with T2DM, although there are indications of a U-shaped association in some populations [19]. Among women, a meta-analysis found birth weights<4 kg were inversely associated with SBP in adulthood, whereas birth weights≥4 kg were positively associated with SBP [20]. Taken together, these studies support that size at birth is associated with CVD and its risk factors through multiple pathways.

## Cardiovascular Disease Risk in Obese Children

In addition to prenatal origins of CVD, childhood is also a period when the risk is further developed. As far too many children are overweight, obese, and severely obese, its impact on the later development of CVD is of major public health importance. As body size in childhood, unlike birth weight, is modifiable, it represents a target for intervention. At the moment, however, a major obstacle to the achievement of successful long-term weight loss in obese youth is the lack of consensus about a systematic treatment.

Although many CVD risk factors may manifest in obese children, overt CVD does not. Instead, the disease process is initiated, and even worsened, by obesity and escalates over the following decades. As such, detecting it early is challenging, although critical for future health. Through autopsies on youth who died from circumstances not related to CVD, fibrous plaque lesions in the aorta were found in children from 2 to 15 years of age [21]. Other autopsy studies have revealed fatty streaks in the larger arteries in children as young as 6 to 8 years, which is one of the first lesions thought to progress to atherosclerosis [22]. These findings indicate that the atherosclerotic process begins in early life, and this likely translates into a higher occurrence of CVD in adulthood.

In the Bogalusa Heart Study, a large prospective study on American youths, associations between body mass index (BMI) (from 5 to 17 years of age) and six CVD risk factors were strikingly non-linear [23]. Among the most severely obese girls (≥ 99th percentile of age- and sex-specific BMI values), 34% had three or more CVD risk factors, whereas few girls below the 99th percentile had more than one risk factor [23]. In this population, the percentage body fat (as assessed by the sum of skinfold thicknesses) was also positively associated with the concurrent presence of CVD risk factors in girls [24]. Other studies have established that insulin resistance is increased in obese youth and that it is exacerbated as BMI increases [25].

The presence of obesity as well as these CVD risk factors in late childhood has long-term consequences. A long-term follow-up of subjects in the Cardiovascular Risk in Young Finns Study found that blood pressure, serum lipid levels, and BMI in childhood were strongly correlated with these values in adulthood [26•], thus establishing the importance of preventing the establishment of adverse levels of these factors already in childhood. A recent study found that childhood obesity, glucose intolerance, and hypertension were associated with premature death (<55 years of age) from endogenous causes, although death due to CVD was rare (accounting for only 22 of 559 cases) [27]. Nonetheless, these results demonstrate that CVD risk factors in childhood have consequences on adult mortality, and thus highlight the importance of identifying and treating these conditions already in childhood.

In Denmark, a recent study showed that approximately 50% of obese children (8 to 14 years of age) referred to a weight loss institution exhibited prehypertension, grade 1, or grade 2 hypertension at referral [28]. During a 3-month weight loss intervention, hypertension was nearly abolished and SBP remained lowered during 28 months of follow-up and continuous weight regain [28]. This was an unexpected and positive long-term effect of a short-term intervention [28]. Earlier larger studies reported hypertension as prevalent in 4% to 15% cases of childhood obesity [29]. More recent studies, however, report higher frequencies of hypertension in childhood obesity [28, 30], which warrants the

term "obesity-hypertension," as the two conditions frequently occur together. In the specialized Children's Obesity Clinic where Danish children and adolescents are treated for obesity [31•], studies have shown that approximately 30% exhibit dyslipidemia and that all forms of cholesterol were beneficially altered with weight loss [32]. In this clinical population, 18% exhibited pre-diabetes and 57% had pre-hypertension, grade 1 hypertension, or grade 2 hypertension (JC Holm, personal communication, 2011). Hypertension in the young is of great concern as it is associated with end organ damage in the heart [33], which likely increases the risk of CVD irrespective of childhood obesity Additionally, 45% of the obese children had>5% fat in their livers [34] and 74% had>5% fat in their muscles [35]. Combined, these studies show that insulin resistance is developing and is accompanied by other independent CVD risk factors in obese children, but that these risk factors improve during obesity treatment [28, 32]. In these studies, there were no apparent sex differences with regard to the resolution of these conditions, which suggests that the reversibility of these conditions is relatively equal between the sexes. Results from these and other studies strongly suggest that the clustering of CVD risk factors in obese children cannot be ignored and must be treated before their future health is further compromised.

## Long-Term Consequences of Childhood Obesity

Given associations between childhood obesity and concurrent adverse levels of CVD risk factors, it is plausible that there are also long-term associations with CVD in adulthood. Already in the early part of the 20th century there was clear interest in how the normative growth of children would affect the occurrence of morbidity and mortality in later life, although most of it focused on the effects of under-nutrition [36]. Since this time, several studies have yielded insights into how body size early in life is related to CVD in adulthood.

Studies on Finnish cohorts have added greatly to the understanding of how body size and growth in childhood may lead to later CVD. In girls born from 1924 to 1933, BMI at the ages of 7 to 15 years was not associated with adult CHD [37] but it was associated with adult T2DM [38]. Additionally, growth (assessed by change in BMI between these ages) was also associated with T2DM [38]. In another Finnish cohort of girls born from 1934 to 1944, a significant trend for an increased risk of adult CHD with increasing BMI at age 11 years was identified [39]. In these girls it was the rate of growth rather than attained body size that was of importance for the future CHD risk. Girls who had a low birth weight and then increased in their BMI z-score from 2 to 11 years of age had an increased risk of CHD as well as raised fasting plasma insulin and pro-insulin concentrations in adulthood [40]. These, and other studies on the Finnish cohorts, indicate that birth weight in conjunction with the pattern of postnatal growth influences the later risk of CVD directly and through the development of key CVD risk factors in women [41].

Studies conducted in other populations examining associations between childhood BMI and CVD have yielded inconsistent results. Studies on a Swedish population yielded tantalizing clues that childhood obesity may increase the risk of future CVD [42, 43], but as the subjects came from a clinical sample, the relevance of these findings to the general population remained unclear. Among British children from 2 to 14 years of age, an association between childhood BMI and ischemic heart disease mortality was found, but not when the sexes were analyzed separately [44]. A study on Scottish children [45] as well as a meta-analysis of cohorts from the United Kingdom [46] did not detect associations between BMI and CHD morbidity and mortality or ischemic heart disease mortality, respectively. Considerable uncertainty thus remained about the associations of body size in youth with the later risk of CVD.

In one of the largest studies to date, the effect of BMI in adulthood was investigated in a cohort of Danish schoolchildren born from 1930 to 1976 [12]. The study included 136,978 girls from the Copenhagen School Health Records Register [47] who experienced 4318 non-fatal and fatal CHD events. Among girls, it was found that the higher the BMI at each age, the greater the risk of CHD. These results held for both fatal and non-fatal CHD, and were little affected by adjustment for birth weight. Of note, the effects were linear, which implies that the risk increased across the spectrum of BMI values and not just above a certain point. Until this time, it was implicitly accepted that there was a threshold effect. These results thus indicated that even moderate degrees of excess BMI increase the risk of future CHD.

Indications of an effect of adolescent body size in girls on CVD came from a landmark study on American adolescents aged 13 to 18 years who were measured from 1922 to 1935 [48]. Among girls, BMI from 13 to 18 years of age was not associated with mortality from CHD or atherosclerotic cerebrovascular disease [48]. As the confidence intervals were wide, these results did not preclude that associations existed, but rather suggested that the study, despite its strong design, was underpowered to detect an effect. A large Norwegian study on adolescents from 14 to 19 years of age who were measured from 1963 to 1975 found increased risks of circulatory disease mortality in women who had low or high BMI values relative to those with a BMI between the 25th and 74th percentiles of BMI-for-age [49]. Results from this study thus indicate that excess body size in adolescent girls also carries a risk for CVD mortality later in life.

Although stroke is a substantial component of CVD, little is known about how childhood or adolescent obesity affects

the risk of this disease. Stroke occurs late in life [3], thus precluding many cohorts from investigating this outcome. Due to the longevity of women, when they do have a stroke it is more severe and more likely to result in death than in men [50]. A nationwide study of American adolescents and young adults from 15 to 34 years of age reported a significant increase in hospitalizations for ischemic stroke from 1995 to 2008 [51]. At the same time, levels of obesity among these patients also increased [51], thus suggesting that body size early in life has immediate consequences for vascular health. In a Finnish cohort born from 1934 to 1944, in analyses adjusted for sex, BMI in childhood at 7 and 11 years of age was not associated with the risk of stroke; rather it was a slow rate of growth from birth until 2 years of age that increased the risk [52]. Other studies have not detected associations between childhood BMI and the risk of stroke in women [45]. Indications of an association between childhood BMI in Danish girls and an increased risk of total stroke (3236 events) were found among 131,604 girls born from 1930 to 1976. At 13 years of age, each unit increase in a sex- and age-specific BMI standard deviation score was associated with a 1.07 (95% CI: 1.03–1.11) risk of having a stroke in adulthood [53]. In a study of American women in the Nurse's Health Study, a mutually adjusted analysis showed that low birth weight increased the risk and that a high BMI at 18 years of age increased the risk of stroke, but interactions were not detected [54]. Similar to CHD, although fewer studies have investigated stroke, the available evidence suggests that body size during childhood and adolescence has long-term implications for its risk.

Until recently, it has remained an unanswered question if remitting from obesity in childhood to a normal body weight in adulthood would reduce the risk of CVD. A study on four international cohorts reported on body size in childhood and adolescence and their associations with the presence of CVD risk factors in adulthood once adult body size was accounted for [55••]. Compared with subjects who were normal-weight as children and non-obese in adulthood, subjects who were overweight or obese as children and obese as adults had an increased risk of having T2DM, hypertension, dyslipidemia, and atherosclerosis. As a corollary to this, however, obese youth who lost weight by adulthood experienced the same risk of CVD as did youth who had persistently been normal-weight. The results from this study demonstrate that there are strong health incentives to normalize weight in obese youth.

## Obesity during the Reproductive Years and the Risk of CVD

The foundations for the future risk of CVD are established in obese children and adolescents. In addition to this, however, are a host of social and behavioral factors that contribute, but these are beyond the scope of this review. Layered on the established CVD risks in overweight and obese girls are the additional risk factors that emerge due to the reproductive capacity that is unique to women.

Obesity in adolescent girls is a risk factor for developing polycystic ovary syndrome (PCOS), particularly among those who are genetically susceptible [56]. It is characterized by metabolic abnormalities such as hyperinsulinemia, increased androgens, and insulin resistance, which are CVD risk factors [56]. Further, the severity of these abnormalities is exacerbated in the presence of excess weight [56]. Women with this syndrome are more likely to experience anovulatory infertility and to convert from impaired glucose tolerance to T2DM [56]. As rates of obesity among adolescent girls are rising, it is anticipated that rates of PCOS will rise as well, and this condition confers risks for the reproductive health of these girls. Among women with PCOS who do become pregnant, they are more likely to develop preeclampsia and gestational diabetes mellitus (GDM), along with other adverse outcomes of pregnancy [57].

Obesity in pregnancy confers a broad range of serious health risks for both the mother and the infant [58]. A normal pregnancy is characterized by a state of progressive insulin resistance [59]. In obese women, this response is even more pronounced, and when combined with defects in pancreatic $\beta$-cell function they are likely to develop GDM [58, 60]. Further, obese women are more likely to develop hypertension [61] and preeclampsia [61, 62] during pregnancy than normal-weight women. To avoid these consequences, in the United States it is recommended that women enter pregnancy at a healthy weight [58]. Meeting this recommendation, however, is challenging as 49% of pregnancies there are unintended [63]. Although slightly lower, 44% of pregnancies in Europe are unintended [64]. With such high rates of mistimed or unplanned pregnancies, in conjunction with high rates of obesity in women of reproductive age, large numbers of women are at risk of experiencing complications of pregnancy.

Aside from immediate risks to the health of the obese mother and her baby, there are long-term CVD consequences for the maternal-infant dyad as well. Women with a history of GDM are more likely to develop the CVD risk factors of T2DM [65] and hypertension many years postpartum [66]. Additionally, these women are approximately 70% more likely to have a later CVD event than women without a GDM-affected pregnancy, although much of this risk was attenuated once subsequent T2DM was accounted for [67]. Nonetheless, results from this study serve to highlight the importance of T2DM in the development of CVD among women. Additionally, women with a history of hypertensive disorders in pregnancy are also more likely to develop T2DM as well as hypertension (independent of the T2DM) many years later [68].

Despite advances in screening and treatment, far too many women experience pregnancies with suboptimal prenatal care, poor nutrition, and a lack of lifestyle modification, which leads to unwanted health consequences for the mother and her child in later life. Alarmingly, there are also long-term negative effects of maternal obesity on the development of CVD risk factors in the infant. Infants of obese mothers are at a greater risk of being born large-for-gestational age [18•], and even of being overweight in adolescence [69]. As these factors are, in turn, associated with an increased risk of CVD, this is another pathway through which maternal obesity negatively affects the health of the next generation.

## Physiologic Complexity Underlying the Mechanisms of CVD Risk

Childhood and adolescent obesity are of paramount importance for predicting the future risk of CVD in women through many pathways. Several acknowledged independent risk factors for CVD in women are established in early life, but their interaction with the obese metabolic risk phenotype throughout the lifespan largely remains to be elucidated. In part, this is because it is difficult to measure the phenomenally dynamic response of complex biological systems in the body that serve to maintain energy balance. Tracking of several important risk factors suggests that the genetic predisposition that influences future health also explains some of the observed risk of disease; however, obesity is a more dynamic phenotype than previously thought [70, 71]. Not all obese children become obese adults, and not all obese adults were heavy as children [72]. Further, not all obese adults become burdened with CVD and a shortened lifespan. Alternately, and very probably, there are genetic or even epigenetic components [73] that underlie the observed associations and influence them in non-obvious directions. Ongoing research in younger cohorts with well characterized biological parameters is likely to yield insights into these mechanisms. Additionally, future longitudinal prospective comprehensive studies combining genetics, the meta-genome, and biological phenotypes translating into obesity and CVD treatment may better elucidate the underlying mechanisms and thus establish specific targets for future prevention and treatment of CVD.

## Future of CVD in Women: Will It Equal That of Men?

Despite the apparent stabilization of obesity in many populations, far too many children and adolescents are overweight and obese. Obesity even exists among pre-school children, with an estimated 43 million classified as overweight and obese worldwide [74]. It is worthwhile to note that historically the childhood obesity epidemic did not develop in a linear fashion; rather there were periods of increases followed by periods of stability in disparate regions of the world [1••]. If these patterns continue, then we could be facing a further increase in the number of overweight and obese girls.

Currently, large numbers of children are already on the path of establishing CVD risk factors. Predictions regarding the effect of adolescent obesity on the future burden of CHD have been made. Although not sex-specific, it is estimated that more than 100,000 additional CHD events attributable to excess weight in adolescence will occur by 2035 in the United States [75]. Worryingly, these estimates are likely conservative due to methodologic considerations [75].

The reproductive capacity of women contributes uniquely to their risk of CVD. Due to the metabolic changes induced by pregnancy with regard to glucose homeostasis, it has been regarded by some as a test of a woman's future risk of CVD [76]. Given the large numbers of pregnancies complicated by obesity and that 7% of all pregnancies (range, 1% to 14%) are affected by GDM [77], as well as the subsequent risk it confers for developing T2DM, there are a substantial number of women who are likely to develop T2DM in the near future. As diabetic women have a three- to fourfold greater risk of developing CVD compared to women without diabetes, this is of great concern [78]. Combined with the longevity of women's lives, the most likely result is that the risk of CVD among women will become equal to that of men.

## Conclusions

Looking into the future, with all of the associated uncertainties, the combination of high levels of childhood and adolescent obesity among girls along with the effects of obesity on reproduction and its subsequent effects on CVD foretells of a rising burden of CVD among women. Life course investigations are needed to fully elucidate how the risk of CVD develops among women throughout their life. Nonetheless, given the numerous pathways through which childhood and adolescent obesity increase the risk of CVD in women and that the risk accumulates across the lifespan, it is entirely plausible that in the future rates of CVD in women will equal those of men.

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