

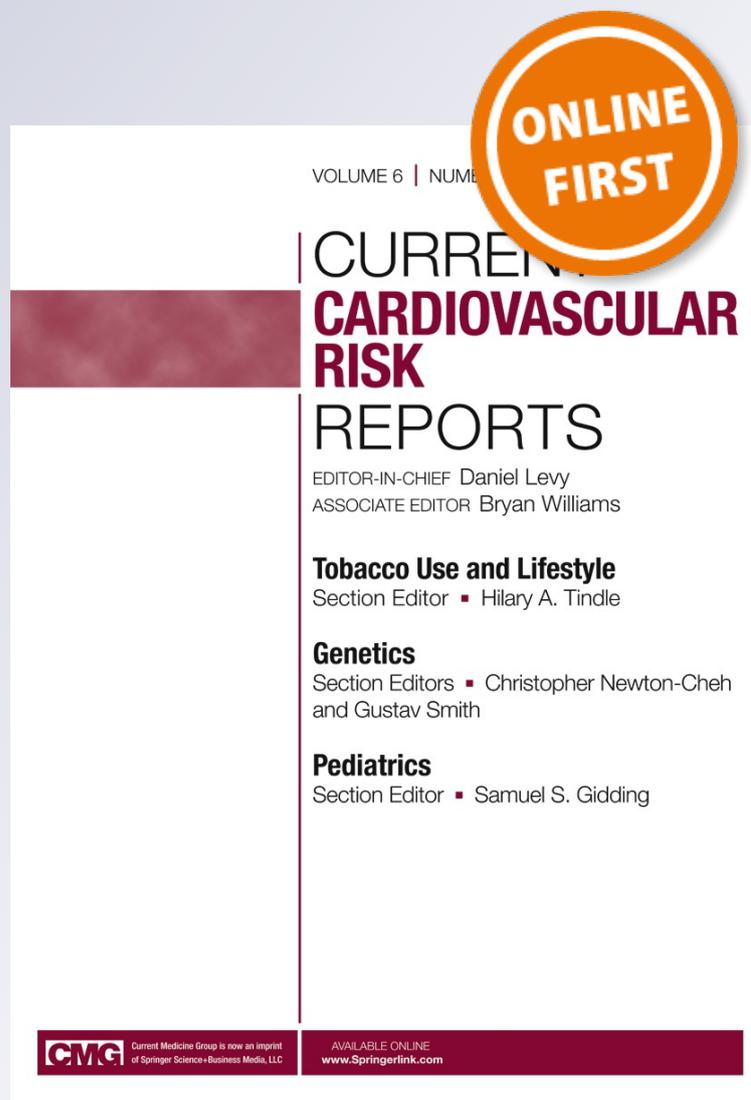
Early Growth Patterns Associated with Cardiovascular Disease

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Early Growth Patterns Associated with Cardiovascular Disease

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Abstract Clearly, the development of cardiovascular disease in adulthood is influenced by growth very early in life, even prior to birth. Substantial evidence indicates that impaired fetal growth and subsequent low birth weight are associated with adult cardiovascular disease and related mortality, and there is emerging evidence that elevated birth weight has similar associations. Patterns of rapid and slow infant growth are each associated with multiple cardiovascular disease processes, and rapid growth during childhood is also predictive of adult cardiovascular disease. Additionally, early adiposity rebound is linked to obesity and diabetes mellitus later in life.

Keywords Cardiovascular disease · Early growth · Birth weight · Infant growth · Childhood growth · Adiposity rebound · Obesity

Introduction

The National Vital Statistics Reports (October, 2012), recently confirmed that cardiovascular disease (CVD) remains the number one cause of death both in the United States and

worldwide [1, 2]. Major prevention efforts are targeted at reducing the risk factors for CVD, including obesity, hypertension, hyperlipidemia, smoking, and type 2 diabetes mellitus. While the bulk of preventive efforts focus on adults, increasing attention is being paid to preventive interventions beginning earlier in life. At least three decades of research suggest that adult cardiovascular disease can be linked to patterns of growth in utero, during infancy, and throughout childhood. The bulk of this data is derived from cohort studies from England or Finland. Within recent years, data from other populations in Europe, North America, and Asia have reinforced these associations. These studies have also identified new early growth patterns associated with cardiovascular disease. Furthermore, new research has begun to identify the mechanisms which link specific patterns of early growth to later cardiovascular disease.

Fetal Growth and Birth Weight

Impaired Fetal Growth and Small for Gestational Age Birth Weight

The fetal origins hypothesis proposed by Barker and colleagues states that CVD is associated with patterns of suboptimal fetal growth which are the result of fetal under-nutrition during gestation [3]. Insufficient nutrition over the course of pregnancy can impair fetal growth to a degree related to the duration of undernutrition. Short-term deficiency results in an underweight, but otherwise normal sized infant, while longer-standing deprivation results in linear growth deceleration, so-called intrauterine growth retardation (IUGR), with the subsequent birth of a low birth-weight or small for gestational age (SGA) infant [4]. IUGR and SGA are generally defined as estimated fetal weight or birth weight, respectively, below the 10th percentile for gestational age [5].

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Since the fetal origins hypothesis was initially proposed, it has been supported by several cohort studies. The associations between low birth weight or SGA and increased cardiovascular risks in adulthood are well-documented. In Finland, low birth weight was clearly associated with higher blood pressure [6–8], type 2 diabetes mellitus [9], and hyperlipidemia [10], after adjustment for confounders such as socio-demographic factors and maternal characteristics. Birth weight has also been shown to be inversely related to CVD mortality in this population [11, 12]. In the U.S., the Bogalusa Heart Study explored the association between birth weight and development of metabolic syndrome in adulthood. This study found that birth weight was inversely associated with the odds of adult metabolic syndrome, even after adjusting for socio-demographic characteristics and body mass index (BMI) in childhood and adulthood [13•]. Similarly, the COHORTS group, which studies children in low and middle-income nations (Brazil, Guatemala, India, the Philippines, and South Africa), found that birth weight was inversely associated with adult glucose intolerance [14••]. SGA is clearly a risk factor for CVD and several of its precursor metabolic abnormalities, and this appears to be true across several populations.

Recent studies have further explored the relationship between SGA and later body mass and body composition. In the U.S., the Project Viva study examined the relationship between birth weight and body size in early childhood. After adjusting for multiple confounders such as gestational age and maternal characteristics, lower birth weight was associated with lower BMI z-score at age 3 [15]. Meanwhile, a Spanish cohort study of Caucasian girls explored the association between birth weight and later childhood body size and composition. This study employed dual-energy X-ray absorptiometry to examine body composition at age 6–10 years. SGA girls and appropriate for gestation age (AGA) girls had similar BMIs in later childhood. However, girls who were SGA were found to have significantly higher truncal ($p < 0.05$) and abdominal ($p < 0.01$) adiposity than girls who had birth weights that were either AGA or large for gestational age (LGA) [16]. The COHORTS group further explored associations between birth weight and later body composition, although this study focused on the linkage between birth weight and adult body composition. In this study, higher birth weight was associated with both higher fat-free mass and fat mass in adulthood, although birth weight was more strongly predictive of adult fat-free mass than fat mass [17]. So, while SGA appears to be associated with increased adiposity in childhood, it was not associated with adiposity in adulthood. It is unclear if this apparent shift from adiposity in childhood to decreased adiposity in adulthood is a pattern associated with all SGA children, or if these differences in adiposity reflect the different populations studied.

Barker and his colleagues proposed a potential explanation for these population-based differences. Specifically, they proposed that a fetal “thrifty phenotype” was best able to preserve fetal growth in the face of undernutrition, but this same phenotype might be less advantageous after birth if food is abundant. Attempts to understand this concept have resulted in interesting research (both human and animal models) with some new insights, further controversy, and without complete resolution [18]. Recent work has also begun to explore the mechanisms through which SGA and CVD are linked via the path of insulin resistance. The linkage between lower birth weight and the development of insulin resistance in adulthood has been established for some time [19]. Additionally, there is evidence that decreasing birth weight is associated with higher levels of glycosylated hemoglobin at the time of birth, suggesting that insulin resistance in these individuals may develop in utero [20]. Building upon that work, a recent Chinese study demonstrated that birth weight was inversely associated glycosylated serum proteins at birth, and in turn, fetal glycosylated serum proteins were positively associated with head-to-abdominal circumference ratio at birth. Glycosylated serum proteins are a surrogate marker for insulin resistance. The authors hypothesize that insulin resistance in utero – whether driven by environmental or genetic influences – may lead to brain-sparing fetal growth and low birth weight. In other words, insulin resistance during gestation may cause impaired fetal growth and subsequent low birth weight. This challenges the concept that impaired fetal growth is a precursor to the development of insulin resistance. This topic deserves further exploration as insulin resistance is linked not only to the development of diabetes, but to other CVD processes including hypertension and dyslipidemia [21].

A new development in the association between SGA and hypertension was reported by Perala and colleagues. Dietary salt intake has long been debated as a possible modifiable risk factor for hypertension and CVD [22]. This study used the Helsinki Birth Cohort to examine whether the effect of dietary salt intake on systolic blood pressure (SBP) was modified by birth weight. For adults with a birth weight ≤ 3050 g, each 1 g increase in daily salt intake was associated with a 2.5 mmHg higher SBP ($p = 0.025$). However, among adults with a birth weight > 3050 g, daily salt intake had no association with blood pressure [23]. This study implies that a lower-sodium diet may have the potential to result in clinically-meaningful reductions in SBP among adults with low birth weight.

Clearly, impaired fetal growth and low birth weight are linked to the later development of CVD and its preceding disease processes such as hypertension, metabolic syndrome, and insulin resistance. Some of these disease processes, particularly insulin resistance, may already be present in utero and may partially drive the impaired fetal

growth that leads to an SGA infant. SGA appears to be linked to increased adiposity in childhood, although not necessarily in adulthood. The linkages between SGA and CVD are fairly well understood in high-income nations, while data from populations in lower-income nations are only recently emerging.

The Role of Prematurity

Low birth weight is generally considered to be the result of one of two phenomena: impaired fetal growth (IUGR) or prematurity, or a combination of the two. Several recent publications attempted to tease out the role that prematurity plays in the later development of cardiovascular disease, independent of impaired fetal growth. A Swedish cohort study explored the association between preterm birth and mortality. After adjusting for multiple confounders including birth weight, gestational age at birth was found to be inversely associated with cardiovascular mortality in early adulthood (CV mortality hazard ratio (HR) 0.93, 95 % CI 0.88-0.99, $p=0.02$, for each one week increase in gestation age) [24]. This suggests that prematurity may have a role in the development of CVD independent of its association with low birth weight. Questions then arise regarding the relative importance of prematurity and impaired fetal growth in the development of CVD, as well as the mechanisms that link prematurity to later CVD.

Three recent studies have attempted to address these questions. The first explored the effect of preterm birth on multiple cardiovascular risk factors in young adulthood, and found that subjects born prior to 36 weeks gestation had higher SBP, pulse pressure, and blood pressure variability (i.e., higher variation in blood pressure over time, which is linked to CVD) in early adulthood after adjusting for confounders including birth weight. However, there was no difference in carotid intima media thickness, an intermediate marker for development of vascular disease [25]. Somewhat conflicting results were presented by Chan and colleagues, who used a retrospective Australian cohort to study similar outcomes in peri-adolescence. In this population, preterm birth was not associated with SBP or arterial stiffness, although prematurity was associated with higher 2 hour postprandial insulin levels. The differences in observations of blood pressure and arterial characteristics between these two studies may be in part attributed to the age difference in the two cohorts. Chan also explored the separate effects of preterm birth and SGA on CVD outcomes. Generally, the independent effect of SGA was more influential over the outcomes (arterial function, renal function, and metabolic function) than prematurity. However, the most significant increases in risk were observed in the subgroup with both SGA and prematurity [26]. This last observation was echoed in a Finnish cohort study. SGA was found to be significantly

associated with higher SBP, LDL, triglycerides, and carotid intima media thickness when compared to AGA. However, prematurity was only found to be inversely associated with carotid intima media thickness. Notably, subjects who exhibited both prematurity and SGA had the most markedly increased carotid intima media thickness in adulthood [27]. Taken together, these results suggest that impaired fetal growth is a more important risk factor for CVD than prematurity alone. However, individuals with both SGA and prematurity are at the highest risk.

Large for Gestational Age Birth Weight

While the relationship between SGA and CVD is fairly well established, possible CVD risks for large for gestational age (LGA, ≥ 90 th percentile for birth weight) infants are emerging. At this time, the data are mixed. Logically, it may be expected that LGA infants would have a higher risk for CVD. LGA infants are frequently born to mothers with gestational diabetes [28]. These mothers also have a higher risk for the later development of type 2 diabetes, so it may be expected that their LGA offspring would similarly have a higher risk for diabetes and other forms of CVD through genetic and environmental links [29]. This has been confirmed in recent studies.

A Greek study demonstrated that LGA was associated with a higher degree of insulin resistance in the prepubertal period compared to AGA [30]. Additionally, a Brazilian study found that LGA was associated with higher blood pressure, central adiposity, and BMI in early adulthood compared to AGA subjects. There were no differences observed in fasting glucose or lipid profiles. Interestingly, LGA subjects with "catch down" growth - a drop in weight SDS >0.67 between birth and age 9-10 years - exhibited lower BMI, waist circumference, and blood pressure in early adulthood than LGA subjects without catch down growth [31].

However, the association between LGA and later CVD may not be that straightforward. The Bogalusa Heart Study, which showed an inverse association between birth weight and later adult metabolic syndrome, specifically observed a protective effect of LGA against the development of adult metabolic syndrome [13]. A similar relationship has also been observed between LGA and central adiposity, which is a key component of metabolic syndrome and an independent risk factor for cardiovascular disease [32]. The Spanish cohort study described above, which observed an increased risk for central adiposity among SGA children, also found that LGA children tended to be larger throughout childhood. However, this increase in body size was proportional and not associated with increased risk for total or central adiposity compared to AGA children [15].

Clearly, the role that LGA may play in relation to later CVD is still being delineated, but LGA is likely associated with some components of adulthood CVD, such as insulin resistance and hypertension. However, LGA may have protective effects against the later development of central adiposity and metabolic syndrome, although the evidence is conflicting.

Immediate Postnatal Growth

Rapid Infant Growth Velocity

Birth weight was the first well-studied early growth risk factor for CVD. During the past decade, significant work has begun to focus on patterns of immediate postnatal growth (from birth until age 2), including both rapid postnatal growth as well as slow postnatal growth. Rapid postnatal growth has been studied most carefully in terms of its relationship to adult hypertension. A systematic review showed that more rapid growth in the postnatal period was associated with higher adult SBP, and this relationship was more pronounced in individuals with lower birth weight who then exhibit more rapid catch-up growth [33]. These results were replicated in a large Finnish cohort study also showing that rapid infant growth was positively associated with blood pressure in early adulthood [6], and similar results were reported in the U.K where more rapid infant growth was associated with higher early adulthood SBP even after adjusting for birth weight [34]. In contrast, Cheung and colleagues observed that rapid growth from 6 months to 18 months of age was inversely associated with SBP after adjusting for confounders including birth weight and gestational age. The authors hypothesize that this apparent conflict with the Finnish study was likely due to the poorer nutrition and socio-demographic status of those in the Chinese cohort. As such, the authors theorize that rapid growth in this population was indicative of adequate nutrition rather than overnutrition [35]. While this study was not designed to answer whether the degree of nutrition in early childhood influenced blood pressure in adulthood, it is an interesting hypothesis which may explain the conflicting associations between early growth velocity and adult blood pressure, and should be further explored.

Several recent papers indicate that rapid postnatal growth is positively associated with multiple cardiovascular risk factors. Using the same Finnish cohort described above, Tzoulaki and colleagues demonstrated that peak weight velocity from birth to 2 years was significantly positively associated with adult blood pressure, weight circumference, and BMI [36]. Similar results were observed in less economically-advantaged populations. An Indian cohort study found that more rapid growth from birth to 2 years

was significantly associated with higher blood pressure and insulin resistance in later childhood [37]. Meanwhile, a Filipino cohort study demonstrated that higher weight velocity from birth to 4 months was associated with young adult BMI and waist circumference, and that weight velocity indirectly affects insulin resistance [38]. Finally, a 2012 meta-analysis of children in primarily economically developed settings found that rapid infant weight gain was associated with obesity later in life. Specifically, each +1 unit increase in SD weight scores from birth to age one was associated with a two-fold increase in childhood obesity, and a 23 % higher risk of adulthood obesity [39]. Rapid infant weight gain appears to be associated with increased risk for CVD in many dimensions and across multiple populations. Infants exhibiting rapid postnatal growth may prove to be important targets for early risk reduction interventions.

Slow Infant Growth Velocity

While ample data support the association of rapid infant weight gain with the development of later CVD, slower-than-average weight gain during infancy appears to also be problematic. Multiple publications from the Helsinki Birth Cohort document the relationship between slow infant growth (specifically, a decrease in BMI z-scores from birth to age 2) and development of coronary heart disease, diabetes, and hypertension in adulthood [7, 40]. In a recent publication, Perala and colleagues examined the post-prandial responses of overweight adults who exhibited slow infant growth compared to overweight adults with normal infant growth. Those with slow infant growth had higher post-prandial triglyceride and insulin responses following a fast food meal [41]. Both rapid and slow patterns of infant growth appear to be associated with increased risk for CVD. It is unclear if these opposing patterns of growth are related to later CVD through two independent mechanisms, or if they are simply different sides of the same coin: sub-optimal nutrition.

Adiposity Rebound

Following infancy, BMI declines until reaching a minimum point in early childhood, and subsequently increases until adulthood. The minimum inflection point of BMI is known as the adiposity rebound [42]. Adiposity rebound (AR) has received significant attention since the observation was documented that children with earlier AR (<5.5 years of age) have a nearly six times higher risk for obesity in adulthood compared to children with later AR (>7 years) [43]. Additionally, early adiposity rebound has been linked to development of type 2 diabetes mellitus [44]. Several

recent studies have begun to expand our understanding of the phenomenon of early AR.

A U.S. study using data from the National Health and Nutrition Examination Survey (NHANES, 1999-2008) demonstrated that adiposity rebound occurred earlier in girls (mean age 4 years) than boys (mean age 5 years). AR also occurred on average 2 years earlier among non-Hispanic African American children compared to Mexican-American and non-Hispanic Caucasian children [45•]. Another study explored the changes in age and BMI at adiposity rebound among different cohorts of U.S. children. They observed that AR occurred earlier among girls born between 1973 and 1999 (a time period in which rates of obesity dramatically increased) when compared to earlier cohorts. Additionally, children born during the obesity epidemic exhibited lower BMI before the AR, and more rapid BMI gain after AR, when compared to earlier cohorts [46]. AR appears to vary according to the time period in which a child is born, as well as by sex, race, and ethnicity; future work in AR will need to take these factors into account.

Childhood Growth

Changes in weight and BMI after infancy also appear to be linked to later CVD, outside of the phenomenon of early adiposity rebound. Rapid weight gain during childhood is a well-established risk factor for subsequent CVD. This association was documented in the Helsinki Birth Cohort, and reinforced in a British cohort. These studies observed that children who were small at birth and then exhibited rapid catch-up growth during childhood were more likely to develop hypertension and type 2 diabetes mellitus in adulthood [8, 47]. Similarly, children with that pattern of rapid catch-up growth had significantly higher rates of adulthood coronary heart disease and cardiovascular mortality [11].

A more recent British cohort, the ALSPAC study, attempted to delineate the relative importance of infant growth and childhood growth on blood pressure and other CVD risk factors. This study found that while low birth weight and rapid infant growth were both influential on blood pressure, rapid growth in childhood (after infancy) had the strongest influence over the development of elevated blood pressure [48••]. Additionally, increases in BMI from age 8.5-10 years were strongly associated with increased LDL, triglycerides, and insulin levels at age 15, although these effects appeared to be mediated through adiposity at age 15 [49]. The Third Harvard Growth study examined the influence of childhood growth on cardiovascular mortality, and found that men were significantly more likely to die from ischemic heart disease if they were ever overweight during childhood [50]. These recent findings underscore the importance of monitoring growth throughout childhood. While risk for CVD

may begin to be established in utero and during infancy, rapid growth and obesity later in childhood carries significant risk in itself.

Conclusion

Early growth patterns are important predictors of cardiovascular disease in adulthood. Low birth weight, rapid infant growth, and rapid childhood growth each have significant evidence to support their link to later CVD. Growth patterns, such as LGA and early AR, are perhaps less understood, but are clearly important CVD risk factors, and future research is needed to better understand their role in the development of CVD. Research on LGA should be prioritized because existing data is somewhat conflicting, and the incidence of LGA infants is likely to increase as maternal obesity and gestational diabetes are becoming increasingly prevalent. We need a better understanding of the disease burden that these LGA infants may carry into their adult life. Early AR is another area which should receive significant focus in future research. While the phenomenon of early AR was described several decades ago, its role as an early marker for later CVD is just beginning to be delineated. Ultimately, the role that early growth plays in the later development of CVD is not likely dependent upon individual growth phenomena such as birth weight and AR alone. It is more likely that the linking of these individual phenomena into growth trajectories – growth curves extending from the prenatal period through childhood – will provide the most comprehensive information linking early growth to CVD.

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- Of major importance

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