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Developmental Origins of Cardiovascular Disease

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Abstract

Although cardiovascular disease has traditionally been viewed as a condition of aging individuals, increasing focus has turned to its developmental origins. Since birthweight has been related to cardiovascular disease risk, research into factors such as gravid conditions that affect fetal growth have grown. Associations between maternal diabetes and childhood obesity from sibling studies suggest a causal role but prospective studies of gestational diabetes remain mixed. Preeclampsia and increased offspring blood pressure has been consistently observed but evidence for other cardiovascular outcomes is lacking. While maternal obesity is associated with childhood obesity, causality remains unclear and paternal obesity should be investigated as an independent risk factor. Environmental chemical exposures *in utero*, particularly obesogens, are now emerging as another concern, as is conception by infertility treatment. Few studies have investigated subclinical measures of endothelial function or atherosclerosis and more research in these areas may help reveal the underlying pathogenesis.

Keywords

developmental origins; cardiovascular disease; birthweight; preterm birth; gestational diabetes; preeclampsia; maternal obesity; environmental chemicals

Introduction

Cardiovascular disease (CVD) and stroke remain the leading cause of mortality in the United States, accounting for 1 in 3 deaths in 2009.[1] With the strategic goal of decreasing

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CVD and stroke mortality by 20% by 2020, the American Heart Association has highlighted the need for "primordial" prevention at the population level, aiming to shift the distribution of CVD risk factors of all Americans rather than relying on individual treatments or secondary prevention.[2] Although smoking, poor diet, and low physical activity are well known modifiable factors related to CVD risk, emerging evidence has pointed to even earlier origins where population-level preventive strategies could be targeted. In particular, prenatal factors have been associated with later childhood or adulthood obesity, diabetes and hypertension, all of which contribute to CVD risk. Therefore, this review serves to summarize the evidence to date for the developmental origins of cardiovascular disease in relation to birth outcomes, pregnancy complications, and other under-researched areas of early life influence.

Birth outcomes

The association between blood pressure in adulthood and birthweight has been noted since the 1980s,[3, 4] and the developmental origins of health and disease hypothesis has become widely accepted.[5] It is hypothesized that fetal adaptations made in response to undernourishment leads to permanent changes in the body's structure and function that increases long-term risks of chronic diseases such as CVD.[6] Since then, many studies around the world have replicated these associations. In meta-analyses, each 1 kg increase in birthweight decreased cardiovascular mortality by 9-15%[7] and decreased systolic blood pressure by 2-4 mmHg[8, 9]. Recently, the Bogalusa Heart Study with detailed data on measured blood pressure from adults aged 19-50 years, further added to the evidence that low birthweight not only increased systolic and diastolic blood pressure but also influenced blood pressure variability suggesting altered regulation.[10]

Nevertheless, findings have been conflicting regarding low birthweight and subclinical markers of atherosclerosis as previously reviewed[11] and among more recent studies.[12-14] Some studies have found positive rather than negative or U-shaped associations with birthweight, suggesting stronger influence of later life over-nutrition or hyperglycemia on later atherosclerotic development.[12] Others have found no association[11], but the modeling of postnatal influences is complex and studies vary in methods used to account for current lifestyle risk factors and in particular, current size. One concern is that current size lies in the pathway from birthweight to CVD risk, such that controlling for the intermediate of current size generates bias in the estimates of the associations. Using more current epidemiologic methods[15], a recent analysis demonstrated that the negative association between birthweight and blood pressure after adjustment for current weight is unlikely to be caused by controlling for the possible intermediate of current weight.[16] Rather, it is likely a direct effect of birthweight on systolic blood pressure not mediated by current weight.[16] Such analyses are reassuring that current size can be accounted for in statistical models.

Another possible explanation for the conflicting findings may be due to differences in treatment of gestational age in analyses as low birthweight may arise due to either preterm birth or growth restriction. In a recent meta-analysis of studies measuring metabolic syndrome factors in adults, systolic blood pressure was 4.18 mmHg higher among the preterm (<37 weeks gestational age) compared to the term group.[17] Increases were also

seen for diastolic blood pressure (+2.57 mmHg) and low density lipoprotein (+0.14mmol/l).[17] However, studies were heterogeneous in methods of selecting on preterm birth and there is a mix of those who were appropriate for gestational age and those small for gestational age which does not clearly tease apart the effect of gestational age from fetal growth. In subgroup analyses, the authors found that the blood pressure association was stronger among studies that recruited based on gestational age rather than birthweight.[17] The Cardiovascular Risk in Young Finns Study is one of the largest cohorts to try to tease these aspects apart. It compared measures of carotid intima-media thickness (IMT) and brachial flow mediated dilation (FMD) at ages 21 and 27 years among a group of 207 participants born small for gestational age (i.e., $<10^{th}$ percentile in birthweight by gestational age), 253 born preterm (<37 weeks gestation) and 835 controls who were born at term and in the normal range of weight for gestational age (i.e., 50-90^{th} percentile birthweight).[14] Brachial FMD was lower and carotid IMT was higher among those born small for gestational age, with similar results among the term and the preterm groups.[14] Both lower FMD and higher IMT are related to greater CVD risk; with FMD being related to endothelial dysfunction and IMT as an indicator of subclinical atherosclerosis.[18] Further study is necessary before a conclusion can be drawn regarding whether preterm birth has an effect independent from birth size.

Even fewer studies have data on fetal growth as measured by ultrasound and postnatal development.[19] However, as recently systematically reviewed, a handful of studies have consistently observed inverse associations between fetal growth measures (such as abdominal circumference) and later systolic blood pressure.[19] Future studies tracking long-term health of children with such data from pregnancy may be helpful for understanding the association between fetal growth trajectory and later health as ultrasound measures are routine in obstetric practice. That increased ability of the fetus to accumulate mass *in utero* as measured by growth velocity may or may not serve as indicator for later susceptibility to a high-caloric, low physical activity environment remains also of interest.

Placental inadequacies resulting in fetal malnutrition have also been implicated in adult cardiovascular disease in offspring.[20] Among 2571 men born in Sheffield, UK, mortality from coronary heart disease showed a U-shaped association with the placental-to-birthweight ratio, the highest mortality being at either end of the distribution.[21] A high placental-to-birthweight ratio also predicted cardiovascular disease mortality among 31,000 men and women in Norway; the sex and cohort-adjusted hazard ratio for the highest versus the lowest third of the placenta-to-birthweight ratio was 1.38 (95% CI: 1.07 to 1.77).[22] The Helsinki birth cohorts have been critical in uncovering several of the relationships between placental size and cardiovascular diseases in adulthood. Among women who were born full-term and compared to those who were longest at birth (>50 cm) but had the lowest placental weight (≤500 g), women who were short at birth (≤48 cm) but had heavy placentas (>700 g) had the highest coronary heart disease hazard ratio of 5.2.[23] These comparisons suggest that a heavier placenta in relation to birth length could be an indicator of fetal malnutrition being inadequately compensated for by placental growth. The association differed by gender. Among men, a low placental weight reflected thinness by a low ponderal index and increased mortality from coronary heart diseases later in life.[24] Altered patterns

of prenatal growth may have subsequent sex-dependent consequences on coronary heart disease risks.

Other characteristics of placental morphology may also serve as indicators of fetal malnutrition.[20] In a study of 2003 subjects, of whom 644 were being treated for hypertension, hypertension was associated with decreased placental weight and surface area at birth.[25] Another investigation of the Helsinki Birth Cohort identified that a thin placenta was associated with increased risk of sudden cardiac death, suggesting impaired autonomic nervous development.[26] Surface area was estimated by the measurement of its two diameters and assumes that the placenta was of elliptical shape. Thickness was then taken to be placental weight divided by estimated surface area. In following up with these observations regarding placental surface area, investigators counted the number of placental cotyledons from photographs of placentas from 910 subjects from a UK birth cohort with measured blood pressure at age 9 years.[27] Contrary to their hypothesis, however, an increased number of cotyledons correlated with increased blood pressure.[27] Such findings suggest there is much to learn about placental morphology and function with fundamental questions remaining related to the mechanisms underlying the placental origins of later heart disease in offspring.[28] Difficulties with measuring accurate placental weight and other morphological features in large epidemiologic studies may remain a research hurdle that should be addressed with particular attention to their methods in study design.

Pregnancy Complications

Not only are the effects of gestational age apart from fetal growth and placental morphology important considerations, upstream causes of each may shed more light on the associations found between birth outcomes and CVD. Moreover, these upstream factors provide opportunities for potential intervention. As such, studies have also investigated associations between CVD in the offspring whose births were complicated by various maternal gravid conditions. Most frequently, studies have focused on gestational diabetes and preeclampsia. Such pregnancy complications could suggest an unfavorable intrauterine environment.

Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset or first detection in pregnancy, occurs in approximately 4-7% of all pregnancies in the US.[29] Epidemiologic studies have shown conflicting evidence for the association between GDM and childhood obesity. Variations in diagnosis criteria, severity, and treatment of GDM and age and measurement of childhood adiposity may at least partly account for inconsistencies of the findings. Most of the evidence of the association between GDM and childhood obesity is from prospective cohort studies or retrospective cohorts with medical record information which are advantageous in not relying on maternal recall of GDM status years after delivery. However, inconsistencies may be partly due to the age of children studied and high attrition rates decreasing statistical power to detect differences [30, 31]. Studies among infants and younger children who may not have experienced their adiposity rebound, do not show any difference in BMI with respect to exposure to maternal hyperglycemia.[32-34] One trial also showed no significant difference in childhood overweight at 4-5 years among mothers actively treated for mild GDM and those who were not treated.[35] The measure of

adiposity may also affect results with one study finding an association using skinfolds[36] but not BMI, while another found a stronger association with waist circumference than BMI [37]. Studies have found that adjustment for prepregnancy body mass index (BMI) attenuates[38] and in some cases eliminates the association altogether[39, 40].

Universal screening for GDM was not recommended until recently, making it difficult to ensure correct classification of exposure status among children born in earlier periods. Moreover, hyperglycemia below the threshold for GDM diagnosis may still prove detrimental for fetal outcomes.[41] Studies have therefore also begun to investigate the level of hyperglycemia during pregnancy rather than comparing only GDM versus non-GDM.[32, 42-44] Of these studies, the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study had the longest follow-up, finding that waist circumference at age seven was significantly associated with continuous glucose measures during pregnancy even after adjusting for maternal prepregnancy BMI.[42]

Studies may be limited by confounding from lifestyle patterns such as maternal diet and physical activity that are shared with the offspring in childhood. Few sibling studies have been conducted to try to address the issue of genetics and shared lifestyle factors.[45, 46] However, neither study was restricted to gestational diabetes. The first was a study among Pima Indian mothers in the late 1990s.[45] Another was recently conducted among 280,866 singleton-born Swedish men.[46] Using record linkages with military conscription data at age 18 years, the men and their brothers were compared for differences in BMI by maternal diabetes exposure with no distinction made between gestational and pre-gestational diabetes. A mean BMI increase of 1.23 (95% CI: 0.11 to 2.36) kg/m^2 was found for the men exposed to maternal diabetes compared to their non-exposed brothers, after adjusting for various risk factors including early-pregnancy BMI. The difference in BMI was attenuated between non-siblings discordant for exposure (0.41 kg/m^2; 95% CI: 0.15 to 0.67) but remained significant, suggesting that the association is neither explained by genetics nor postnatal environmental exposures but rather strongly related to the intrauterine environment. However, associations for GDM or lower levels of hyperglycemia remain untested.

With regards to other cardiovascular disease indicators and GDM, a meta-analysis found that GDM was associated with slight increase in systolic (+1.39 mmHg) but not diastolic blood pressure in offspring measured in childhood or adolescence.[47] Findings regarding lipid metabolism have been divided with some finding no association[42, 48] and others detecting a difference,[30, 37] although associations may be driven by concurrent findings of increased childhood BMI. One study from Hong Kong found no differences in arterial stiffness among 42 GDM-exposed adolescent offspring at age 15 years compared to 87 controls.[49] However, cord blood levels of c-peptide were positively associated with carotidfemoral pulse wave velocity (i.e., an indicator for arterial stiffness) and other vascular measures.[49] More studies are needed on the endothelial function of children exposed to GDM.

Preeclampsia

Preeclampsia is generally defined as new onset hypertension during pregnancy accompanied by proteinuria after 20 weeks of gestation, although no consensus exists for its diagnosis and

its pathogenesis remains unclear.[50] It can affect 2-8% of pregnancies and is the leading cause of both maternal and perinatal mortality and morbidity.[50] Similar to GDM, maternal obesity is a known risk factor for development of preeclampsia making prepregnancy BMI a potentially strong confounder of any relationships with childhood CVD risk. As earlier delivery at 34 to 36 weeks occurs frequently for pregnant women with preeclampsia[51], associations with offspring CVD risk factors may be mediated by gestational age. Davis et al. systematically reviewed studies available up to August 2011 and determined by meta-analysis of 12 studies that blood pressure is elevated among offspring (aged 4-30 years) born to women who had preeclampsia compared to controls (+2.39 mmHg SBP and +1.35 mmHg DBP).[52] In sensitivity analysis restricted to four studies with information on gestational age, findings remained similar for term infants of normal birthweight.[52] Offspring BMI also differed (+0.62 kg/m^2) by preeclampsia status and a few studies showed increased triglyceride and lower HDL cholesterol.[52] Since Davis' meta-analysis, findings from two long-term longitudinal studies with measures at age 16 years[53] and at age 17 years[54] further confirmed positive associations with blood pressure. Gestational hypertension without preeclampsia was also found to increase childhood blood pressure.[53, 54]

With regards to endothelial dysfunction, a pilot study of 26 mother-child pairs with preeclampsia compared to 17 without measured reactive hyperemia after occlusion of the brachial artery among children at age 5-8 years.[55] No differences were found by preeclampsia status but rather a lower reactive hyperemia index was found among those born SGA (which included cases and controls). However, larger studies are needed to replicate these findings. Some research hurdles include difficulties in classifying preeclampsia severity and time of diagnosis may play a role in how the fetus is affected.

Maternal adiposity

Associations between maternal adiposity and childhood obesity have been systematically reviewed.[56] Although many studies have shown an association, some doubt has been cast on whether the association is purely due to genetic or shared environmental effects.[57-59] One argument is that maternal obesity should have stronger associations than paternal obesity if "programming" occurs due to prenatal influences of increased maternal adiposity on the fetal endocrine system, or other structures. Observations that associations are similar in magnitude between paternal and maternal BMI and risk of childhood obesity then suggest that the associations are due to shared postnatal lifestyle.[58, 59] What is not clear is whether paternal adiposity plays a distinct role in "programming" as well. Preliminary evidence in a mouse model suggests that paternal diet induced obesity transmitted obesity through two generations of offspring with epigenetic changes detected.[60]

Adding to the complexity of this association is that obesity may be associated with many different nutritional influences. Most epidemiologic studies have used gestational weight gain as a proxy for over-consumption during pregnancy. The amount of gestational weight gain through pregnancy is the sum of three primary components involving maternal tissue, placenta, and fetus.[61] A study of ~140,000 sibling pairs found that maternal fat gain (measured by the difference between postnatal weight and weight at first clinic assessment) among overweight and obese women was associated with a small increase in offspring BMI

at age 18 years (0.06 kg/m2; 95%: 0.01-0.12) with no additional contribution of weight gain among normal weight women.[62] Timing of the weight gain may also be important to decipher with greater effects on offspring development found for weight gained prior to the third trimester in one study.[63] Fetal weight makes a greater contribution to third trimester weight while earlier weight gain is more likely to reflect maternal fat stores. In terms of specific dietary factors, evidence remains insufficient for dietary recommendations during pregnancy directed at limiting childhood obesity,[64] although some suggestions of fatty acid consumption on later offspring adiposity have been observed.[65, 66]

Environmental Exposures

Evidence implicating environmental exposures on risk of cardiovascular disease is accumulating. Most notable is tobacco smoke, considered to be the most preventable cause of cardiovascular disease.[67] A well-established link also exists between long-[68] and short-term[69] exposure to ambient air pollutants and CVD. The evidence for long-term exposures increasing cardiovascular mortality risk is strongest for fine particles, elemental carbon and nitric oxides[68] which commonly result from traffic and other combustion sources. Exposure to other environmental chemical exposures from common sources such as pesticides or plastics is also fairly ubiquitous [70] and many of these chemicals can directly or indirectly influence the risk of cardiovascular disease.

That the fetal cardiovascular system is affected by maternal smoking has long been recognized.[71] More recently, the National Toxicology Program reviewed the evidence regarding its positive association with childhood obesity, concluding it is most likely causal.[72] Too few epidemiologic studies, however, have studied secondhand smoking exposure in relation to offspring cardiovascular disease risk factors. A study of over 74,000 pregnant Norwegian women between the ages of 14-44 years, found that *in utero* tobacco smoke exposure (i.e., during their mothers' pregnancy), was associated with increased odds of obesity (OR=1.53, 95% CI:1.45-1.61), hypertension (OR=1.68, 95% CI:1.19-2.39) and gestational diabetes mellitus (OR=1.32, 95%CI:1.10-1.58)[73]. This study suggests that smoking exposure may have trans-generational effects through other pathways even if smoking itself is discontinued in the next generation.

Numerous studies have linked risk of preterm delivery and growth restriction to maternal exposure to air pollution and environmental chemicals (e.g. persistent organic pollutants such as polychlorinated biphenyls (PCBs), metals such as lead, non-persistent chemicals such as bisphenol-A).[74, 75] As discussed earlier, these birth outcomes have long-term implications on cardiovascular disease risk and health. Whether there is an independent direct effect of early life air pollutant exposure on subsequent CVD risk is unknown but, developmental effects or "programming" of respiratory anatomy and function by early life air pollutant exposure has been suggested, perhaps as a result of oxidative stress[76]. Cognitive effects have also been proposed as a result of the pro-inflammatory responses common in children exposed to air pollution such as high levels of inflammatory cytokines and associated tissue remodeling and regulatory immune responses[77]. As such, evidence from the respiratory and neurodevelopmental literature suggests that adult cardiovascular disease may also share early life air pollution exposure risk driven by the developmental

effects of inflammation and oxidative stress. This understudied area merits further investigation.

Other exposures may act on offspring CVD risk indirectly, particularly by increasing obesity risk. Some environmental chemicals can act as endocrine active compounds that either mimic or interfere with the normal function of hormones. A fast growing area of research is the identification of "obesogens" or environmental chemicals, such as phthalates[78] and bisphenol-A[79] that may promote obesity through mechanisms of lipid regulation and adiopogenesis. Prenatal exposure to PCBs has been associated with heavier children [74] and changes in offspring growth and development have been observed for both prenatal and lactational exposure.[80] Similar to the notion of fetal "programming" derived from maternal nutrition, these chemical obesogens may result in permanent changes not detectable until later in life. These changes can impact the function and response of hormones which can ultimately promote obesity in the offspring.[81] Two systematic reviews evaluated the evidence for the association between environmental chemicals and increased adiposity from chemical exposure at various ages.[82, 83] Most studies found a significant positive association between adiposity and the organochlorine insecticide, dichlorodiphenyltrichloroethane and its metabolite. Research in this area is complicated because effects of environmental chemicals on growth and development may not follow traditional monotonic dose-response curves, the response may differ between offspring and parents, or *in utero* effects may not be evident until adulthood.

To our knowledge, prenatal chemical exposures have not been studied in association with markers of atherosclerosis or other hard CVD outcomes in offspring. However, adulthood exposure to bisphenol-A was associated with severity of coronary artery disease as measured by angiography in one cross-sectional study of 591 adults from the UK.[84] Whether there are persistent effects from *in utero* exposure remains to be seen and the impact of environmental chemical exposures on cardiovascular disease health outcomes and co-morbidities should not be overlooked.

Infertility treatment

Infertility treatment, particularly assisted reproductive technologies (ART), is associated with higher risk of preterm birth and low birthweight along with pregnancy complications.[85] As its worldwide use has been increasing[86-88], conception by ART may serve as an important risk factor for later cardiovascular risk. Three of five studies have found that children conceived by infertility treatment have higher blood pressure than those conceived without treatment.[89] Two studies found increased carotid IMT among children conceived by ART compared to controls (measured at 6 months[90] and at 11 years[91], respectively) along with other vascular differences. One of the studies compared children who did not differ by gestational age or birthweight[91], whereas the other study included 17 low birthweight children in the ART group compared to one child in the control group and adjusted for birthweight percentile along with gestational age and preeclampsia.[90] Epigenetic alterations to vasculature due to ART treatment, perhaps resulting from *in vitro* culture, sperm selection or ovarian stimulation, has been hypothesized to be an underlying mechanism behind the observed vascular differences[91, 92]. Methylation patterns of

placental and cord blood samples significantly differ among those conceived by ART and those not, particularly for genes in the adiposity and metabolic pathways[93]. These methylation differences require confirmation and larger studies with longitudinal follow-up are necessary to better understand whether these observations persist through the life course and are not confounded by shared lifestyle factors or a common cause associated with underlying infertility.

Conclusions

More remains to be done to identify the “primordial” risk factors and inter-generational effects that can be the next frontier of modifiable CVD risk. Women planning pregnancy may be strongly motivated to make lifestyle changes that will benefit the long-term health of their offspring. However, the impact of the paternal contribution should not be dismissed. Whether observed associations are truly causal will remain a difficult task for epidemiologists to decipher but new techniques to tease apart direct and indirect effects to understand the individual contributions of birth outcomes, their preceding gravid conditions and the broader influences of nutrition and environmental exposures appear promising. In spite of the complexity of the causal relationships between pregnancy complications, parental obesity and CVD outcomes in the children, those complications may serve as a vehicle to help identify children at high risk.

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