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PERINATAL ORIGINS OF CARDIOVASCULAR HEALTH DISPARITIES ACROSS THE LIFE COURSE

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The World Health Organization has declared a “life-course approach” to be essential for achieving the population health goals of the United Nations 2030 Agenda for Sustainable Development. Because of increasing evidence linking intrauterine exposures with future disease risks, action must focus on preconception, pregnancy, fetal development, and the most vulnerable life stages.¹ However, despite a growing recognition of the long-term effects of early-life stressors, little attention has been given to their potential role in the origin of health disparities across the life course. New evidence suggests that racial/ethnic disparities in cardiovascular disease (CVD) might be linked with similar disparities that exist in preterm birth. We hypothesize that perinatal stressors are important factors underlying both the development of CVD later in life and racial/ethnic disparities in CVD.²

Prior studies have shown that CVD may originate early in life due to environmental exposures in childhood and adolescence. Low socioeconomic status (SES) in childhood has been linked with behavioral risk factors such as poor diet and obesity that track into adulthood, potentially leading to hypertension, diabetes, and CVD. In addition, higher allostatic load and systemic cortisol levels in response to chronic psychosocial stress may also contribute to early development of atherosclerosis. Subclinical atherosclerotic changes have been detected in adolescence and are more common in racial/ethnic minority and low SES groups. In response to such evidence, the American Academy of Pediatrics has asserted that “many adult diseases should be viewed as developmental disorders that begin early in life, and that persistent health disparities associated with poverty, discrimination, or maltreatment could be reduced by the alleviation of toxic stress in childhood.”³

Increasingly, the origins of CVD are now traced even earlier than childhood, to the preconception and perinatal periods. Barker’s theory of developmental origins was first published over 20 years ago, and postulated that intrauterine nutritional abnormalities and

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growth restriction may result in fetal programming for subsequent development of cardiometabolic disorders. Intrauterine growth restriction has been associated with an increased risk of CVD later in life, and potentially may contribute to racial/ethnic disparities in CVD because it is more common in black infants. The underlying mechanisms are an intensive area of ongoing research, but experimental and clinical evidence suggests a role of epigenetic modification of neuroendocrine responses to stress.²

More recent evidence suggests that developmental programming on the background of preterm birth may be particularly important for long-term outcomes. Preterm birth interrupts normal development of all fetal organs and has been linked with chronic disorders affecting multiple organ systems in adulthood, including cardiometabolic, respiratory, and neuropsychiatric diseases.⁴ Prematurity has been associated with increased stress reactivity, vascular stiffness, and impaired angiogenesis, leading to hypertension, endothelial dysfunction, and development of atherosclerosis. In addition, it predisposes to impaired glucose metabolism, potentially from multiple causes including reduced mass or function of pancreatic β cells which are formed predominantly in the third trimester of pregnancy, exposure to antenatal corticosteroids, and rapid catch-up growth in infancy leading to visceral adiposity and insulin resistance. The combined effects of these cardiometabolic changes may increase the risk of CVD in preterm-born adults.

Preterm birth has previously been linked with several major risk factors for CVD later in life, including hypertension, type 2 diabetes, and metabolic syndrome. Surprisingly, despite these associations with CVD risk factors, most studies of preterm birth in relation to ischemic heart disease (IHD) have been null or inconclusive, possibly because of insufficient follow-up of large cohorts into adulthood. However, new evidence from a population-based cohort of over 2 million people with up to 43 years of follow-up indicates that people who were born preterm have a ~40% increased risk of IHD in early to mid-adulthood.⁵ After adjusting for sociodemographic and maternal factors, relative risks for IHD at ages 18–43 years associated with preterm (<37 weeks) or early term (37–38 weeks) birth were 1.44 (95% CI, 1.19–1.73) and 1.16 (1.02–1.31), respectively, compared to full-term birth (39–41 weeks) (Figure 1). Co-sibling analyses further suggested that these associations were not explained by shared genetic or environmental factors in families, but instead were likely from direct effects of premature birth.⁵ These findings from the largest cohort to date suggest that persons born prematurely have a significantly higher risk of IHD that may emerge in early to mid-adulthood. Their longer-term risks in later adulthood are still unclear and will require additional follow-up to older ages. Large studies in the US and other diverse populations are also needed to further explore for heterogeneity among different racial/ethnic groups. In addition, information on lifestyle and other environmental exposures later in life would be useful to elucidate factors that modify the effects of preterm birth on CVD risks.

These new findings linking preterm birth with CVD may have important implications for CVD disparities in the US. We hypothesize that racial/ethnic disparities in CVD might be linked with similar disparities that exist in preterm birth. Despite improvements in CVD mortality over the past few decades, it remains the leading cause of death in the US, and substantial racial/ethnic disparities persist. CVD mortality rates among blacks and whites

began diverging in the 1970s, as mortality steadily declined among whites, but plateaued or declined more slowly among blacks. As a result, the black-white ratio of CVD mortality rates increased from 1.04 in 1968 to 1.21 in 2015. Modest improvements in these disparities have occurred in the past few years. However, continued improvement is uncertain because of persistent large disparities in major risk factors for CVD, especially hypertension, which remains significantly more prevalent and less likely to be treated effectively in blacks. Socioeconomic and institutional barriers to health care access contribute to these disparities.

Racial/ethnic disparities in CVD and its risk factors may also be related to similar disparities that exist in the prevalence of preterm birth. In the US, preterm birth is ~50% more common among blacks (13.3%) than whites (8.9%).⁶ A large meta-analysis found that after adjusting for potential confounders such as SES, maternal age, parity, and marital status, blacks still had twice the odds of preterm birth compared to whites (pooled odds ratio, 2.0; 95% CI, 1.8–2.2).⁶ The underlying reasons are not established but may involve the effects of chronic psychosocial stress on neuroendocrine, inflammatory, and epigenetic mechanisms that are related to preterm delivery.

Unfortunately, public health efforts to reduce preterm birth and its disparities in the US have been largely unsuccessful. The overall prevalence of preterm birth in the US is currently 10%, near the estimated worldwide prevalence of 11%. In contrast, the prevalence in Canada and most European countries that have universal health care, including those with diverse populations, is 5–8%. Most of these countries also experience lower CVD mortality rates.⁷ Effective strategies to reduce preterm birth are urgently needed and may potentially reduce downstream effects on CVD and its antecedents, though this remains to be demonstrated. Such efforts should include better access to preconception, prenatal, and postpartum care among high-risk women, as well as reduction of non-medically indicated deliveries before full-term. More comprehensive provision of primary care for minority women is an essential priority for reducing racial/ethnic disparities in preterm birth and its long-term health sequelae.

Despite the importance of a life-course approach, it is seldom well-integrated in clinical practice. Perinatal origins for CVD disparities have several clinical implications. For patients of all ages, perinatal and childhood history should be routinely obtained, including gestational age at birth, birth weight, perinatal complications, as well as adverse childhood events. Such information can provide essential context for understanding patients' long-term health and help trigger more intensive early interventions to reduce other risk factors across the lifespan, such as obesity, hypertension, diabetes, and smoking. Preterm-born children and adults are a high-risk group who need long-term follow-up for preventive actions and anticipatory screening for CVD and its risk factors. Targeted outreach that addresses multiple CVD risk factors is more likely to be effective than narrower interventions, and should be prioritized in high-risk and underserved communities.

An emerging body of evidence indicates that CVD disparities in adulthood may originate in the earliest stages of life. These disparities may be related to persistent racial/ethnic disparities in preterm birth, which has been linked with future development of CVD, other chronic disorders, and premature mortality.^{4,5} Alleviation of toxic stress not only in

childhood but prenatally and in the earliest stages of development may help reduce lifelong disparities in these outcomes. Current strategies to address disparities in adulthood thus require reframing to encompass the earliest stages of life. Implementation of such a life-course approach in public health and clinical practice will be essential for achieving better and more equitable health in the US.

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Figure 1.

Adjusted hazard ratios for ischemic heart disease (IHD) by gestational age at birth compared to full-term birth, Sweden, 1973-2015.