Developmental Origins of Hypertension: Biology Meets Statistics

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The concept that environmental factors during development—both in utero and in early childhood—can permanently alter the adult phenotype derives from the seminal epidemiologic observations of Professor David Barker (1). He and his colleagues showed in the early 1990s that low birthweight predicted increased risk of cardiovascular diseases, including insulin resistance/diabetes (2–4), obesity (5), coronary disease (6), and, importantly, systolic hypertension (3,7,8). Birthweight was used as a readily available, albeit crude, surrogate for adequacy of fetal growth. While these early observations have now been confirmed in studies around the globe (9,10), the link between birthweight (BirthWt) and systolic BP (SysBP)—both its presence and its significance—has continued to generate controversy (11,12). The typical finding in adults has been an inverse relationship between BirthWt and SysBP (9) that is independent of—but enhanced by—accelerated childhood growth (7). The existence of this relationship in white adults, not always apparent in studies with limited maternal information (12), was recently confirmed in 31-yr-old subjects from a large prospective and broadly annotated North Finland birth cohort (13). While the differences in average SysBP across the birthweight range are typically small, their cardiovascular impact is predicted to be large based on modern hypertension treatment trials (e.g., [14]) and based on a similar inverse relationship of BirthWt and prevalence of clinical hypertension (15). The mechanisms linking BirthWt and adult SysBP are not known, but reduced nephron number (16), fetally programmed activation of the postnatal tissue renin/angiotensin II (AngII) system (17), and enhanced vascular reactivity to pressors (18) and stress (19) have each been implicated.

In experimental models, it is abundantly clear that impaired fetal growth can lead to altered BP regulation, often in pubertal offspring (20). However, in humans, it is not yet clear at what age the SysBP effects of fetal programming become manifest, especially since the inverse BirthWt:SysBP relationship may be weak or absent in children, especially adolescents (21). Because the inverse relationship is strengthened with aging in adults (15,22), the variability in children may indicate that developmentally programmed hypertension requires cofactors that emerge only later in life. In the existing literature, there have been no large, prospective, cohort studies that include standardized BP measurements in children.

In this issue of JASN, Hemachandra et al. report on the relationship between BirthWt and SysBP at age 7 yr in a large, multicenter, US cohort of children born full-term between 1959 and 1965 (Collaborative Perinatal Project) (23). This database (now in the public domain) is exceptionally large (n = 29,710) and racially balanced (approximately 50% black). The major finding reported is that black children exhibited an unexpected positive BirthWt:SysBP relationship, whereas white children showed no significant relationship. The racial difference is robust and is not diminished by adjustment for current weight (CurrentWt) or by adjustment for childhood weight gain over age 4 to 7 yr (see adjustment issues below). The pattern observed in blacks mirrors findings of Rostand et al. (24) in a small and selected group of 5-yr-old subjects in Alabama, in which black children also exhibited a positive relationship between BirthWt and SysBP. In contrast, the white children in the latter study showed an inverse correlation.

Despite the cohort size and convincing racial disparities, the report by Hemachandra et al. may not fully resolve for white children the question of whether a true inverse relationship is present at age 7 yr. This relates to perhaps the stickiest controversy surrounding the BirthWt:SysBP relationship, a statistical phenomenon known as the “reversal paradox” or “statistical suppression” (25,26). This phenomenon argues that statistical adjustment in multivariate regression (e.g., the BirthWt:SysBP relationship) for a third factor that lies in the etiologic pathway (e.g., current body mass index [BMI] or weight) has the potential to create a spurious inverse relationship that has no biologic relevance. Importantly, this statistical adjustment for current body weight in multivariate regression emphasizes the effect of change in body weight (BirthWt versus CurrentWt), and does not precisely assess separate effects of the two parameters (26). Whether this adjustment is appropriate or confounding may well depend on the specifics of the cohort (12,25). A consideration of the biologic complexities now known to underlie fetal growth restriction is instructive in pondering that question as well as the decision of Hemachandra et al. to avoid adjustment for current weight.
In a unique longitudinal Helsinki cohort providing annual growth data for all children in the cohort, both a lower BirthWt and an accelerated increase in BMI in childhood independently increased the risk of adult hypertension (7). While this database could not address whether impaired fetal growth was causal in the later growth acceleration, both human and animal studies strongly support an etiologic link (27). That is to say, global caloric restriction in rat dams leads to hyperphagia and excess food intake ("thrifty phenotype") in offspring, together with accelerated weight gain and excess fat mass (28) under ad libitum conditions. In microswine offspring after maternal protein restriction, similar hyperphagia and accelerated growth on ad libitum intake precede sustained hypertension (Du Priest et al., unpublished observations, 2006). In South African children who were born small and subsequently exhibited rapid growth, weight gain was preferentially deposited as central fat rather than lean tissue (29). Thus, altered fetal nutrition/growth impacts not only fetal but also postnatal growth trajectory when postnatal food is available. There is, then, after intrauterine growth restriction, a fatally programmed distortion of the normal BirthWt:CurrentWt relationship, and this varies depending on the nutrient availability in postnatal nutritional environment. The argument to adjust or not to adjust for CurrentWt overlooks this complexity, since neither option statistically accounts for these biologic interactions. Keizjer-Veen et al. (26) have suggested an alternative statistical approach that accounts independently for the BirthWt effect and for the effect of postnatal growth exceeding that expected based on BirthWt alone (as BirthWt and CurrentWt normally have a positive relationship). Thus, "current weight residuals," the difference between BirthWt and predicted versus actual CurrentWt, are used to factor for CurrentWt and are independent of BirthWt. This approach specifically accounts for the presence (or absence) of the programmed distortion of the BirthWt:CurrentWt relationship without the potential confounding inherent in simply adjusting for current body weight. While beyond the scope of this commentary, the approach (26) provides a compelling argument that our statistical methods must evolve along with our biologic knowledge.

Hemachandra et al. include, for purposes of comparison, a CurrentWt-adjusted analysis and find that white children in fact convert from a neutral to a significantly inverse BirthWt: SysBP relationship, while black children convert from positive to neutral (23). While choosing to accept the BirthWt:SysBP relationship without CurrentWt adjustment, thereby avoiding the "reversal paradox," Hemachandra et al. do not employ alternative approaches that would more appropriately factor for CurrentWt effects on SysBP. So, while it is possible that white 7-yr-olds are in fact simply too young to exhibit an inverse BirthWt:SysBP relationship, it is also not possible to definitely exclude this idea as currently analyzed.

This raises a final feature, unique to the Collaborative Perinatal Project, which should inform interpretation of BirthWt:SysBP patterns and racial differences (23). The most striking feature of this cohort of pregnant mothers was the prevalence of poverty as determined using 1960 to 1970 criteria: 39% in whites, 72% in blacks, 54% overall. These mothers were remarkably thin, and, in a culture that predated cheap fast food, were likely consuming considerably fewer calories than would be the case today in a financially comparable US population. If limited prenatal nutrition induced programming, and continued postnatal calorie deficit with persisting poverty prevented programmed acceleration of childhood growth, then the cohort overall might have a considerably weakened inverse BirthWt:SysBP relationship as compared with 7 yr olds in a nutrient-rich postnatal setting. As a result, the findings in this low-income population, while representative of an unfortunately growing segment of the US population, might not be generally applicable to more affluent US children. Moreover, with respect to racial differences, black mothers exhibited twice the poverty rate of whites and, perhaps not surprisingly, were more anemic. Accordingly, more severe calorie deficits pre- and/or postnatally, or a higher prevalence of specific nutrient deficits known to exert programming effects independently of birthweight (e.g. iron [30]), may have played a role in black offspring independent of genetic factors.

From a broader perspective, these issues highlight the increasingly recognized insensitivity of BirthWt as a surrogate for fetal growth/nutrient adequacy (12). Fetal growth restriction, as manifested by the thin infant with its asymmetric growth phenotype, occurs within the normal BirthWt range. Moreover, as suggested above, specific nutrient deficits can program permanent effects (e.g., nephron number via prenatal glucocorticoid [31] or BP via maternal iron [30] or calcium [32]) without modifying overall body/organ growth patterns. As Gillman has emphasized, understanding and detecting the specific underlying mechanisms—independent of BirthWt—are crucial to our future ability to identify mothers and infants at risk for fatally programmed hypertension (12).

In summary, Hemachandra et al. have provided an important contribution by defining, in a large prospective US cohort, racial discrepancies in the BirthWt:SysBP relationship that are already apparent at age 7 yr. Whether these robust differences are genetic, socioeconomic/environmental, or an interaction between the two is not yet clear, since other differences between the groups could potentially explain the findings. Taking heed of these results, future studies should be designed to differentiate environmental from racial/genetic factors given their disparate implications for therapeutic intervention. As future reports from the Perinatal Collaborative Project are forthcoming, it is hoped that new statistical approaches that account for the biologic complexity of programming effects will add to our understanding of growth patterns and BP profiles in children destined to be come hypertensive.

References


See the related article, “Racial Disparities in the Association between Birth Weight in the Term Infant and Blood Pressure at Age 7 Years: Results from the Collaborative Perinatal Project,” pages 2576–2581.