It Takes Three to Tango
Genes Complicate the Association Between Birth Weight and Cardiovascular Disease

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The risk factors of cardiovascular disease (CVD) are thought to be well known, but the relative importance of nature versus nurture continues to be debated. Although sex, family history, and genetic susceptibility are recognized as playing a major role, most attention has focused on lifestyle risk factors because of the substantial clinical benefits achievable—and achieved—by preventing or treating hypercholesterolemia, diabetes mellitus, hypertension, obesity, and smoking. In addition to genetically determined and postnatal risk factors, during the past 2 decades, developmental programming has emerged as a potential determinant of CVD. The concept that adult CVD is influenced by the conditions encountered by the developing fetus in utero originated largely from the observation by Barker and colleagues1 that low birth weight was associated with increased CVD. This prompted a flurry of epidemiological studies, the majority of which supported the association of birth weight with CVD and hypertension,2,3 whereas the association with type 2 diabetes mellitus remains more controversial.4–6 Later studies highlighted the need to differentiate low birth weight resulting from premature birth from true intrauterine growth restriction and established that the CVD risk is in fact associated with birth weight adjusted for gestational length.7

Unfortunately, the original Barker hypothesis has yielded only limited mechanistic insights and no translational benefits as of yet. The difficulty in identifying the underlying mechanisms stems largely from the fact that birth weight is an outcome of pregnancy and does not result from a uniform pathogenetic condition in utero. Epidemiological studies of populations born during prolonged hunger periods established undernutrition as a cause of low birth weight,8 but many other pathogenetically diverse factors can result in low birth weight, such as severely protein-deficient diets, mechanical obstructions of the uterine artery, corticosteroid treatment, and gestational diabetes mellitus. Some of these have been replicated in experimental models, but interpretation of results is complicated by the fact that they do not consistently reduce weight in all offspring.9 Until recently, the hypothesis also promised few clinical benefits, because postnatal compensation for low birth weight actually increased CVD.10 It is now possible to raise birth weight in cases of severe early-onset intrauterine growth restriction, but whether such prenatal intervention affects adult CVD remains to be established.11

The problems associated with using an outcome parameter of pregnancy, the recognition that other maternal factors affect in utero programming of CVD independently of birth weight, and the fact that overnutrition rather than undernutrition poses the greater health risk in better-off countries are beginning to lead developmental programming research away from low birth weight and toward specific pathogenetic factors encountered by the fetus in utero.12 Nevertheless, low birth weight has recently been adopted as a risk factors of CVD by the World Health Organization, and investigations into its causes may still yield insights into the mechanisms of in utero programming. Epidemiological studies using twins are particularly useful for this purpose, because co-twin–control analysis allows the exclusion of the influence of factors shared by both twins. In this issue, Öberg and colleagues at the Karolinska Institute in Stockholm report the compelling results of a large population-based co-twin–control study that provides important insights.13

In this study, the association between birth weight and CVD was assessed in monozygotic and dizygotic twins by comparing same-gender co-twins who were discordant in CVD (n=3884), coronary heart disease (n=2668), or stroke (n=1372) morbidity or mortality. In agreement with many previous studies in singlets, a significant inverse association between birth weight and CVD was observed in dizygotic twins with an odds ratio of 0.73 per 1-kg birth weight increase (95% confidence interval, 0.57 to 0.92). Separate analysis of coronary heart disease and stroke yielded similar results. In striking contrast, no significant associations between birth weight and CVD, coronary heart disease, or stroke were seen in monozygotic twins. This is incompatible with the assumption that impaired intrauterine growth per se is sufficient to increase CVD later in life. Clearly, other factors must be involved, but what could they be?

The factors determining CVD in general and those that could have affected results in monozygotic and dizygotic twins in the present study are shown in the Figure. If one neglects postnatal risk factors, which did not differ significantly between co-twins, and focuses on the factors that may affect in utero programming, 3 major groups come to mind. The first group, maternal factors, includes those previously identified as potential causes of low birth weight, eg, severe undernutrition or dysnutrition, corticoid treatment, and ges-
tational diabetes mellitus. It also includes maternal factors that may not affect birth weight but for which there is solid evidence of an effect on offspring atherosclerosis, endothelial function, increased oxidative stress, immune functions, altered glucose metabolism, or other surrogate parameters of adult CVD.14–17 For some of these factors, eg, maternal hypercholesterolemia, evidence for a protective effect of interventions in mothers has also been provided.17,18 At first glance, none of these maternal factors should affect programming of CVD in twins, because both co-twins would be subjected to the same influences. It is possible, however, that the susceptibility for some pathogenic maternal factors is genetically determined. In this case, otherwise identical maternal factors may cause different effects in genetically different dizygotic twins but not in genetically identical monozygotic twins.

The second group of factors are placental ones. Maternal dysmetabolic conditions are known to alter placental gene expression and function, and may influence the transfer of pathogenic factors from mother to fetus such as excess cholesterol.19 However, this would not affect twins exposed to the same maternal factors. In contrast, placental factors independent of the mother could play a role. Monozygotic and dizygotic twins may differ in placentation, and consequently in the degree to which they share or compete for blood, oxygen, and nutrient supply. In particular, the greater likelihood of separate (dichorionic) placentas in dizygotic twins may contribute to greater differences in birth weight, and therefore favor statistical association. It is also possible that low birth weight reflects tissue or organ immaturity and that this persists over time and enhances CVD, just as pulmonary immaturity predisposes to asthma. Nevertheless, placental effects on both birth weight and CVD seem to be an improbable explanation for the complete lack of association between birth weight and CVD in monozygotic twins because they would occur in both monozygotic and dizygotic groups, albeit to different extents.

The factors most likely to be responsible for the striking difference between the monozygotic and dizygotic groups are genes. Genetic differences between dizygotic co-twins may include genes governing the susceptibility to maternal pathogenic factors (discussed above), genes influencing fetal development and growth, and genes predisposing to CVD independently of developmental programming. Obviously, co-twin analysis would reveal differences only if one of the dizygotic twins has such susceptibility genes, and the overall association in the dizygotic group would underestimate their effect in individual pairs. In monozygotic twins, one would expect interpair differences in CVD, depending on whether both twins have or lack the susceptibility gene(s). More important, though, co-twin–control analysis of genetically identical monozygotic twins would not be influenced by genetic factors, and would therefore not show an association between birth weight and CVD, consistent with the findings of Öberg and colleagues.

In summary, the results provide no support for an association between birth weight and CVD in the absence of genetic differences. For the association to be evident in the general population, genetic factors must be present that differ between dizygotic twins but are shared by monozygotic twins. This may explain the discrepancies between past epidemiological studies carried out in ethnically different populations or in cohorts more diverse than the fairly homogeneous Swedish one. The apparent need for genetic cofactors may
also appear to weaken the case for developmental programming in the sense that the in utero environment may not be enough to program CVD later in life. One should keep in mind, however, that the present study only tested the original Barker hypothesis tied to birth weight and does not prove that genetic cofactors are necessary for in utero programming by maternal factors that are independent of birth weight. In fact, some of these factors have been confirmed in genetically uniform murine models and therefore do not require genetic cofactors.12 On the other hand, there is no reason to believe that the effect of factors independent of birth weight could not be amplified by genetic factors. On the contrary, there is increasing evidence from genetically uniform models that developmental programming is indeed influenced by both the in utero environment and genetic factors.20 Although the loss of the “pure” environmental hypothesis should not be lamented, an involvement of genetic factors will certainly complicate therapeutic translation. Altogether, the involvement of genes is not surprising. Very little is known about the mechanisms responsible for developmental programming,12 but many of the putative mechanisms involved, including epigenetic programming, involve both genes (or gene transcription mechanisms) and environmental factors that may affect them, eg, increased methylation or acetylation. The present study should help to elucidate these mechanisms by emphasizing the importance of using genetically uniform experimental models. Conversely, comparing CVD programming between genetically different models or humans may identify relevant genes. Ultimately, there is no better argument for the further investigation of developmental programming than the fact that CVD stubbornly holds its place at or near the top of the list of major causes of morbidity and mortality, and the most effective current treatments reduce it by less than half.

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References

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