Invited Commentary

Invited Commentary: Timing and Types of Cardiovascular Risk Factors in Relation to Offspring Birth Weight

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Birth weight is associated with later-life cardiovascular risk. A new study by Romundstad et al. (Am J Epidemiol 2007;166:1359–1364) challenges us to consider influences on birth weight with respect to timing and type. Timing of effects on birth weight, according to the “fetal origins hypothesis,” is in utero. Alternatively, familial aggregation—genetics or shared environment—may explain birth weight and suggests prepregnancy influences. The Romundstad et al. findings support familial effects: maternal metabolic factors predicted birth weight for gestational age. However, because maternal physiology sets the fetal environment, these data do not necessarily counter the fetal origins hypothesis. Types of maternal metabolic influences demonstrated by Romundstad et al. include elevations in blood pressure being associated with lower birth weight for gestational age, whereas unfavorable glucose and lipid levels were associated with higher birth weight. These findings are consistent with the authors prior hypothesis that vascular dysfunction and metabolic profile (glucose and lipids) have divergent effects during pregnancy. Moreover, these new data underscore that both extremes of birth weight may be related to cardiovascular risk. Few data sets contain prepregnancy, pregnancy, and childhood information. Without all such time points, life course effects will remain only partially understood. It is hoped that studies such as the forthcoming National Children’s Study will generate critical understanding of this issue.

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Don’t try to make children grow up like you or they may do it. Russell Baker

Life course epidemiology is the study of the links between adult health and physical or social exposures acting during gestation, during childhood, or across generations. A proliferation of studies demonstrates the profound impact of influences prior to birth on later health. A marker of these earliest effects is birth weight. Yet, our understanding of the determination of birth weight is beset by uncertainties about the timing and types of critical exposures.

Understanding the timing of exposures is critical to determining when in the life course interventions would be most meaningful. One camp, those ascribing to the “fetal origins hypothesis,” argues that key exposures occur during fetal life. These in utero insults, sometimes termed “in utero programming,” acting alone or interacting with later modifiers have lifelong effects on structure, function, and ultimate health. In particular, fetal nutritional deprivation, with concurrent growth restriction, is posited to produce individuals with a “thrifty phenotype” who hold onto nutrients and, should food be plentiful, later develop metabolic syndrome (central adiposity, glucose intolerance, hyperlipidemia, and hypertension). The several lines of evidence for this hypothesis include historical semieologic studies linking starvation to later morbidity (1); association between small birth size, accelerated childhood growth, and adult disease (2, 3); animal experiments involving starvation and overfeeding (4, 5); and natural history studies showing that diabetic women have diabetic offspring (6), particularly when glucose intolerance has affected the pregnancy. The fetal origins hypothesis suggests that interventions to improve health during pregnancy and early childhood are critically important.
FAMILIAL AGGREGATION OF RISK FACTORS

Another camp argues that familial aggregation may explain associations between birth weight and later health. Familial aggregation represents the intergenerational similarities in health explained by genetic or shared environmental factors. Heavy mothers have heavy children, and underweight mothers have thin offspring (7, 8). Similarly, mothers and fathers who are hypertensive, diabetic, and hyperlipidemic have children who grow up with these same propensities. But does this familial aggregation explain life course observations and in particular that small-for-gestational-age babies are more likely to have elements of metabolic syndrome later in life? It may, if metabolically at-risk mothers, who are well known to have metabolically at-risk children, have babies that are either too small or too large. Then, perinatal outcome and later-life phenotype might both relate to a common familial susceptibility. That is, what appears to be in utero programming resulting in immediate extremes of birth weight and later metabolic syndrome might be attributable to at-risk mothers being poor pregnancy carriers and also having at-risk children.

The evidence for this is, first, that heavy mothers and fathers are more likely to have babies who are at both extremes of the birth weight distribution. The propensity for diabetic mothers to have large-for-gestational-age (macrosomic) babies is well known (9). Overweight mothers are also at elevated risk of having low-birth-weight babies (10). Thus, the mother’s propensity toward metabolic syndrome and the child’s likely propensity to the same are jointly connected to extremes of birth weight distribution.

Second, the epidemiology of preeclampsia supports a model of familial aggregation. Mothers entering pregnancy with the elements of metabolic syndrome are at excess risk of developing preeclampsia. Preeclampsia is a known risk factor for fetal growth restriction and also fetal macrosomia (11). Preeclamptic mothers and their offspring are more likely to have cardiovascular disease later in their respective lives (12, 13). Finally, preeclampsia risk is elevated among sisters and daughters, but not among relatives by marriage, of preeclamptic mothers (14). That is, preeclampsia is intergenerational and is linked to metabolic syndrome both before and after pregnancy, as well as to birth weight extremes, all suggesting a pattern of familial aggregation. Moreover, the fact that cord blood from fetuses of preeclamptic pregnancies does not seem to indicate that these fetuses are underfed, and indeed may be exposed to an excess of nutrients (15), is inconsistent with a fetal deprivation model.

Third, mothers who have low-birth-weight babies, even in the absence of preeclampsia, are also at elevated risk of later cardiovascular disease (16, 17) and metabolic syndrome (18). Similarly, the fathers of underweight children are, albeit less so than the mothers, at elevated risk of cardiovascular disease (19).

Fourth, mothers who were small at the time of their own birth are more likely to bear babies who are small for gestational age, again supporting an intergenerational effect on cardiovascular risk (20, 21).

Fifth, twin studies have shown that cardiovascular outcomes are more highly associated with the experience of the other twin and less associated with birth weight than would be expected if the critical period were in utero (22, 23), although this “confounding by familial aggregation” has recently been challenged (24). Thus, several lines of evidence suggest that cardiovascular risk aggregates in parents and children and that at-risk mothers have small babies, consistent with intergenerational effects. The familial aggregation hypothesis suggests that interventions to improve health before pregnancy are critically important.

IMPORTANCE OF TIMING AND TYPES OF EXPOSURES

How can we discriminate between fetal origins and familial aggregation? It has been difficult in the absence of prepregnancy information. Without it, one must impute or deduce preexisting maternal risk. To our knowledge, the new study by Romundstad et al. (25) is the first to demonstrate that maternal pathophysiology prior to pregnancy impacts birth weight for gestational age. Specifically, both prepregnancy blood pressure and prepregnancy metabolic profile influenced perinatal phenotype. Previous studies relied on data during and after pregnancy or those recalled from before pregnancy. In establishing temporality, the current data more credibly support a familial effect on birth weight. They also suggest associations that are relatively strong. For example, the adjusted effect of a maternal prepregnancy systolic blood pressure of $\geq 129$ mmHg resulted in infants weighing, on average, 72 g less than the referent group of infants born to mothers whose systolic blood pressure was $<100$ mmHg. The magnitude of this effect was similar to that associated with current smoking, considered the single most preventable cause of reduced fetal growth. However, fetal origins and familial aggregation need not be an either-or. Maternal predisposition likely directly alters the in utero environment. We recently hypothesized that maternal vascular dysfunction results in abnormal placentaion and predisposes to growth restriction and preeclampsia (26). That is, hypertension prior to pregnancy alters placental development within pregnancy, likely depleting nutrient transport to the fetus. Both the fetal origins and the familial aggregation camps may be “right.”

This brings us to the other basic question in life course epidemiology: what types of exposures exert what types of influences on birth weight? In the Romundstad et al. study (25), higher blood pressure prior to pregnancy was associated with lower birth weight for gestational age, whereas unfavorable levels of lipids and glucose (here termed “metabolic profile” as distinct from metabolic syndrome, which includes hypertension) were associated with higher birth weight for gestational age. That blood pressure and metabolic profile are mechanistically distinct in their life course effects is consistent with our hypothesis that maternal vascular dysfunction results in abnormal placentaion and predisposes to growth restriction and preeclampsia (26), a hypothesis that has a further component. We also argued that growth restriction and preeclampsia diverge in their association with metabolic profile. Metabolic profile appears to be associated with preeclampsia but be protective against growth restriction. Perhaps, as Romundstad et al. suggest, it is the

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balance between blood pressure and metabolic profile that determines which babies will be large and which small.

The Romundstad et al. paper (25) thus contributes to questions of both timing and types of effects on birth weight, a critical marker for later-life health. Just as importantly, this new contribution demonstrates the import of examining maternal prepregnancy physiology. It is no small task to dissect the influence of specific exposures from the complexity of other exposures over a life course. Even more difficult is doing so with patchy life course data. As one example, the metabolic syndrome commonly observed among women with prior preeclampsia may be the result of a prepregnancy predisposition to metabolic syndrome or due to the pathophysiology of preeclampsia itself (27). An optimal life course data set would include health information from a child’s mother and father prior to conception, antenatal and intrapartum data, and interval health information during childhood and adolescence. Such data sets are vanishingly few or nonexistent. Given the increasing evidence that health patterns are determined very early in life, more replete life course information is critically needed.

Enter the National Children’s Study. This study plans to examine prospectively mothers and fathers prior to pregnancy and during pregnancy and then to follow their children for decades. This repository of rich, longitudinal health information has the potential to address many remaining questions in life course epidemiology. Insights from the National Children’s Study may well help to clarify and isolate the timing and types of influences early in life that influence the development of later morbidity and therefore inform appropriately timed interventions to improve long-term health. Tune in over the next decades for future updates in life course epidemiology.

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