Invited Commentary

Invited Commentary: Interpreting Associations Between High Birth Weight and Later Health Problems

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High birth weight (>4.0 kg) has been associated with a wide range of health problems later in life. The interpretation of these statistical associations may be difficult, however. These difficulties are closely linked to methodological challenges in this research, such as filtering out confounding from family factors, disentangling associations with prenatal processes from associations with postnatal processes, and uncovering what birth weight actually represents. The well-conducted study by Kristensen et al. (Am J Epidemiol. 2014;000(0):000–000), presented in this issue of the Journal, offers an interesting example of how one can filter out confounding from family factors. In an elegant series of analyses, the authors show how an apparent inverse association between birth weight and later intelligence among those in the highest range of the birth weight scale became a positive association when proper adjustment for family factors was made. Sibling comparisons were important here.

birth weight; health; intelligence; siblings

Abbreviation: IQ, intelligence quotient.

The awareness of possible negative consequences of excessive fetal growth is not new. The higher risk of birth complications has long been acknowledged (1). During the second half of the previous century, the characteristic reverse J–shaped association between birth weight and perinatal death was replicated in many populations (2), showing a steep decline in mortality rates with higher birth weights in the low and middle ranges of the birth weight scale, as well as higher mortality rates in the highest range of the scale. During the last 2 decades, however, interest in the potential health risks associated with high birth weight (>4.0 kg) has soared, and statistical associations between high birth weight and the risk of negative health outcomes have been presented in many scientific papers (3–8). High birth weight has been associated with a wide range of health problems later in life, such as overweight and obesity (3), type 2 diabetes mellitus (4), psychiatric disorders (5, 6), and cancer (7, 8).

Interpreting associations between high birth weight and the occurrence of health problems later in life may be difficult, however. These difficulties are closely linked to major methodological challenges in this research, such as 1) filtering out confounding from family factors; 2) disentangling associations with prenatal processes from associations with postnatal processes; and 3) uncovering what birth weight represents.

The well-conducted birth cohort study by Kristensen et al. (9), presented in this issue of the Journal, offers an interesting example of how one can filter out confounding from family factors. The authors explored the shape of the association between birth weight and later intelligence quotient (IQ) score. As the authors document in their introduction (9), previous population studies have rather consistently shown a positive association with intelligence in the low and middle ranges of the birth weight scale. But in the highest range of the scale, the association between birth weight and IQ score has, for unclear reasons, tended to be negative. The unexplained lower IQ scores associated with high birth weights were the focus of this study by Kristensen et al. (9). The authors had at their disposal a file with excellent register data on Norwegian men who had been examined at birth and again at the time of military conscription. The authors restricted the study population to men who were born at 37–41 weeks of gestation, and they additionally adjusted for the length of pregnancy.
Thus, birth weight in this study was a proxy for intrauterine growth. In an elegant series of analyses, the authors showed that with increasing levels of control for background factors, the inverse association between birth weight and IQ score in the highest range of the birth weight scale turned into a positive association. The sibling comparison showed that the mean IQ score of men with birth weights of 5,000–6,660 g was 2.2 points higher than the mean IQ score of their brothers with birth weights of 4,000–4,499 g. The authors also showed that, at a given birth weight, men who had a sibling with macrosomia had, on average, lower IQ scores than men who did not have siblings with macrosomia. This family tendency explained, to a large extent, the striking difference between the results from the individual-level analysis and those from the comparison of brothers. The within-sibship association between birth weight and IQ score in the upper range of the birth weight scale was not linear, though. As the authors put it, there was “rather low robustness in coefficients” for these very high birth weights. The authors mention these concerns in their discussion and explain that the relatively low number of persons with high birth weights included in the sibling comparison caused “obvious power limitations.” Even so, this study suggests that, in Norwegian singleton males born at term during the years 1967–1976, the apparent negative association between high birth weight and later IQ score that is seen in individual-level analysis may be explained by confounding from family factors.

Sibling comparison is a powerful method to filter out family-level confounding (10–12). It is particularly helpful when used along with individual-level analysis, as in the study by Kristensen et al. (9). The interpretation of the results may not be straightforward, though (10, 13). The sibling comparison approach is based on the assumption that the estimates of the within-sibship association are free from confounding from all factors that are shared by the siblings, such as cultural background and parental characteristics (13). However, although siblings are born to the same mother and usually raised in the same family, their experiences and exposures during intrauterine life and childhood may differ in many respects. Some of these nonshared factors may confound associations between birth weight and later health outcomes. For example, maternal health and maternal knowledge of (and attitudes toward) nutrition may change from one pregnancy to another and may influence the children during prenatal and postnatal life. Such nonshared confounding may represent a major challenge to the interpretation of within-sibship estimates (13). Frisell et al. (13) concluded that within-sibship estimates may be more severely biased by nonshared confounding than are ordinary unpaired estimates. Donovan and Susser (10) described another aspect of the sibling comparison design that may also represent an interpretation problem. This is the fact that sibling comparisons not only adjust for environmental factors, but also, to some extent, for genetic predisposition. Many of the genes we inherit from our parents have also been inherited by our brothers and sisters. The effects of such genes that are shared by siblings are among the factors that are adjusted for in sibling comparisons. Thus, when we discover a large difference between the results of an individual-level analysis and the results from a sibling comparison, we may not know whether the confounding that is filtered out by the sibling comparison is caused by genes or family environment (10).

When we try to make sense of associations between high birth weight and later health or intelligence, we are also confronted with the fact that there is a connection between intrauterine growth and childhood growth or weight gain. Although postnatal catch-up growth may occur (14), there may also be a positive association between birth weight and growth or weight gain during childhood. For example, in 345,856 Norwegian singleton men who were born at 37–41 weeks of gestation without physical anomalies during 1967–1984, there was a J-shaped association between birth weight and linear growth from birth to young adulthood (height at military conscription minus length at birth) after adjustment for gestational age at birth (W.E., unpublished data, 2014). Men with birth weights of 2,500–2,999 g had the least postnatal growth, and for higher birth weights, postnatal growth increased with increasing birth weight. In 15,852 Chinese boys and girls, there was an exponential association between birth weight and the odds of overweight or obesity at 3–6 years of age (15). These associations between birth weight and childhood growth or weight gain are not necessarily results of direct cause-and-effect relations. One may imagine, for example, that a gene coding for a hormonal growth factor acts in a similar way during childhood as it does before birth. Therefore, if postnatal growth processes have effects on later health or intelligence, they do not necessarily act as mediators of the effects of intrauterine growth. Because growth and weight gain during childhood have been associated with later health problems and later intelligence (16–21), we may be uncertain as to whether an association between birth weight and later health or intelligence is the consequence of prenatal or postnatal processes. For example, one can imagine that an association between high birth weight and the occurrence of type 2 diabetes in adulthood might actually be caused by an association between high childhood weight gain and later diabetes. Although Kristensen et al. (9) did not address this aspect in their study, it does not undermine their findings and conclusions. However, we are left with uncertainty as to whether the positive association between birth weight and later intelligence is the consequence of prenatal or postnatal processes. One cannot discount the possibility that high birth weight in this study might be, to some extent, a marker of high childhood growth.

Interpreting associations between birth weight and later health or intelligence also involves efforts to uncover what birth weight actually represents. Assuming that the strength of gravity is the same everywhere on the surface of the earth, birth weight may be considered an expression of the baby’s mass. Mass is often visualized as the amount of “matter” or the amount of “stuff” (22). In the science of physics, mass is a physical property with 2 distinct and measurable manifestations or aspects (23): the gravitational mass, which is reflected in the force exerted on the body caused by gravity; and the inertial mass, which is reflected in the body’s resistance to changing its state of motion. The problem is that, irrespective of which aspect of mass we examine, an infant’s mass does not give any information about the morphological, physiological, or biochemical conditions in the infant’s body. Obviously, a small muscular baby may
have the same mass as a larger, less muscular one, and a life-
less piece of gold may have exactly the same mass as these
babies. Thus, from a life science perspective, and from a
medical point of view, the relevance of an infant’s mass is
not obvious. It is hard to imagine that this physical property
of the baby could be causally related to later health or intelli-
gence. Several authors have come to similar conclusions
(24, 25). The mass may, indeed, be correlated with other
physical properties of the infant, and these properties may
be the subject of interesting hypotheses and interpretations.
But then, of course, we move away from a causal role for
mass itself. In the study by Kristensen et al. (9), for example,
gestational age-adjusted birth weight may be a proxy for
intrauterine growth of the brain is certainly rele-
vant here, but it is not identical to the baby’s mass.

Statistical associations between high birth weight and later
health or intelligence are hard to interpret. Yet, they are inter-
esting findings because they may elicit ideas and intriguing hy-
potheses about how events and processes during intrauterine
life may determine important aspects of a person’s later life.

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