Commentary: Birthweight and childhood cognition: the use of twin studies

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It has long been recognized by obstetricians and paediatricians that babies of lower birthweight experience an increased risk of some physical and mental morbidities soon after birth and in childhood.1 Additionally, over the past two decades, the formulation of the ‘Developmental Origins of Health and Disease’ (Barker) hypothesis2 has resulted in acceptance that pre-natal influences (usually captured by birthweight) have a much longer reach than previously anticipated. Much of this research has concentrated on somatic illness—cardiovascular disease, cancer, their risk factors—but it has more recently been recognized that cognitive ability (itself a risk factor for these outcomes3) in childhood and beyond may also be influenced by early life characteristics.4 Indeed, Barker has suggested that the understanding of the causes and consequences of cognitive function will be one of the three big contributions from fetal origins research, the others being obesity and longevity.5

Previous studies have shown a positive association between birthweight and intelligence, in both singletons and twins. In singletons, there is a small but statistically significant association that appears not to be fully explained by potential confounding factors such as socio-economic position.4 Twin studies provide a particularly powerful study design in this regard because, in principle, they implicitly control for the pre- and post-natal environment. A comparison of dizygotic with monozygotic twins allows the genetic contribution to a given characteristic to be quantified. Previous twin studies have shown conflicting results, with some suggesting that there is a direct relationship between birthweight and IQ,6 whereas others indicate that this is not the case.7 Therefore, there is a need for further well-powered twin studies—such as that by Torche and Echevarria8 in the present issue—to further investigate the complex links among genetic factors, the pre- and post-natal environment and intelligence, in childhood and beyond.

Torche and Echevarria8 describe a twin study using a large sample of individuals (n = 220 062 with 2474 twins) born between 1998 and 1999, and tested in fourth grade (around the age of 9 years). That the study was based in Chile (a middle-income country with wide social inequality) is particularly relevant in a literature dominated by cohorts drawn from affluent nations. The use of routinely collected administrative data—unusual in countries with a developing infrastructure—prevents recall bias in birthweight. This study is also to be commended in using different statistical methodologies that attempt to establish the impact of weight differences both in twin births (where a common genetic and extra-uterine pre-natal environment is assumed) and singletons. The authors test for an interaction between the pre-natal environment and post-natal opportunity (estimated by maternal education), and find that lower birthweight is more strongly associated with cognitive ability at the age of 9 years in children whose mothers have less education relative to those who were well educated. This adds to the debate about early childhood intervention to improve social and cognitive outcomes,4 suggesting that such initiatives may have the most impact on public health if they target children of mothers who have been relatively disadvantaged.

Torche and Echevarria’s findings8 add to the increasing evidence that the ‘cognitive cost’ of being a twin seems to have disappeared in cohorts born more recently. Thus, in studies whose members were born between 1921 and the 1950s, twins scored about five IQ points (about one-third of a standard deviation) lower than singletons.6 However, more recent studies have shown this difference to disappear in modern European cohorts’ whose members have experienced improved social circumstances...
(particularly after the world wars), nutrition and healthcare. Torche and Echevarria show that in 9-year-olds born in 1998–99, the cognitive cost of being a twin is between a fifth and an eighth of a standard deviation, but that this difference is eliminated when twins and singletons are matched on important birth, maternal and societal characteristics. This suggests that growth-restricted singletons are neither positively nor negatively selected, and that these findings can be extrapolated to the wider population, not just restricted to twins (up to 4% of all births). In addition to comparing twins with singletons, studies also consider the determinants of birth weight and IQ differences within twin pairs. There is a suggestion of an IQ difference within monozygotic twin pairs (around one-fifth of a standard deviation), implicating intra-uterine environmental exposures, rather than genes or family environment, whereas others have found the opposite, suggesting that genetic factors mediate part of the association between birthweight and childhood IQ. Torche and Echevarria find a stronger effect of intra-uterine growth on IQ in monozygotic than dizygotic twins, which suggests a stronger effect for environment (such as nutrient intake due to umbilical cord insertion and uneven placental sharing) than genetics. The diverse results from different studies in this area suggest that a systematic review and meta-analysis of twin data would improve our understanding of the relative importance of genetic and environmental factors on birthweight and IQ in twin studies.

There are inevitably a few minor caveats we would raise about the contribution of Torche and Echevarria; the total number of births eligible for inclusion (denominator) is not reported, therefore the extent of selection bias due to exclusion of births/children with incomplete information cannot be estimated. Zygosity status is estimated (as opposed to directly measured), although the rationale and implications are well discussed. Cognition was based on the use of Maths and Spanish fourth-grade results provided the exposure is prevalent, even small effect sizes can have a significant impact—as is the case for low birthweight in resource-poor countries—and intra-uterine growth may be amenable to intervention whereas genetic factors are not. The finding that intra-uterine environment and later social circumstances interact raises the possibility of targeting intervention at the most at risk groups.

Improvements in information technology should allow better information exchange between countries at disparate stages of the economic transition. Torche and Echevarria show the benefit that can be derived from analyses of routinely collected data. We believe it is essential that high-quality routinely collected data at the population level should continue to be archived and made available (with appropriate ethical scrutiny) to researchers to allow testing of existing hypotheses. It is important that studies using similar methodologies, e.g. twin studies, also use similar statistical methods to allow comparison between studies, ideally using individual-participant meta-analysis. Emerging statistical approaches—emerging, at least, in the field of epidemiology—such as structural equation modelling may allow investigation of inter-related effects that may be on the causal pathway to the outcome of interest. Such multidisciplinary working, not only methodologically and statistically in epidemiological studies, but also in translational research with basic scientists and clinicians from a range of disciplines, is key to improving understanding of the mechanisms underlying these associations. Although the effect size of the impact of birthweight on cognition in childhood is, as discussed, of low magnitude, and appears to be decreasing with time, studies such as this demonstrate that pre-natal influences can have long-lasting effects, interacting with later life circumstances, and suggest that twin studies can still contribute to our understanding of influences on later health, even in the ‘post-genomic’ era.

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**References**


