In this issue of the *IJE*, Huang *et al.* present an investigation into the roles of birthweight and postnatal growth in cognitive and behavioural development in a sample of Chinese children. No associations were found between birthweight or postnatal growth measures and behavioural outcomes and we therefore limit our discussion to the cognitive outcomes. Importantly, this study addresses the question of the relative influence of the intrauterine vs ‘extra-uterine’ environment (i.e. pre- and post-pregnancy maternal circumstances) in determining cognitive development. To do so the authors compare the strength of association between birthweight and a marker of cognitive development (IQ) and between postnatal anthropometric growth markers and IQ in both term and preterm children. Their findings suggest a positive association between birthweight and cognitive ability among term children, with effects only slightly attenuated with adjustment for potentially confounding factors including family socioeconomic status and mother’s IQ. A similar association was reported between postnatal growth and IQ among term children, although this effect was attenuated by nearly 50% with adjustment for other factors. Birthweight was found to be relatively more important for IQ compared to postnatal weight gain; the effect of a 1-SD increase in birthweight on IQ was approximately double that of a 1-SD increase in postnatal weight gain, although both effects were small (<2 IQ points). The association between postnatal growth and IQ is problematic to interpret given that both exposure and outcome were measured contemporaneously at 4–7 years of age and detailed developmental trajectories were not available to allow temporal ordering of growth in anthropometric and cognitive dimensions.

Among preterm births in this sample, no relationship was found between birthweight and cognitive ability, which is perhaps not surprising given the multitude of factors which may affect premature labour and delivery. Among these children, however, postnatal weight gain was positively associated with IQ, although this association was not robust to covariate adjustment and again suffers from the limitations of a cross-sectional design. It is likely that, in addition to the alternate mechanisms posited by Huang and colleagues (e.g. family socioeconomic status), the preterm analyses were underpowered to estimate the ‘true’ effect. Further, catch-up growth may be relatively more important in preterm children within the early postnatal period and effects may be less pronounced by 4–7 years of age. In short, Huang *et al.*’s findings appear to most clearly support the link between birthweight and cognitive development in term children, although a similar link between postnatal weight gain cognitive development in preterm children can not be ruled out.

In this commentary, we assess the interpretation of birthweight as a marker of intrauterine growth and the maternal-foetal environment, provide historical context to the birthweight-cognitive development studies and discuss some alternative study designs for future research to consider causal relationship of birthweight/postnatal growth on cognitive development in children, and more generally other outcomes in children.

**Birthweight and cognitive outcomes among children: an overview**

Although there exists a considerable literature on the relationship between low birthweight and cognitive outcomes, there is now also interest in examining...
whether this association holds for children born in the normal weight range (i.e. >2500 g). A review and meta-analysis of the birthweight-cognitive ability association concluded that the included studies seemed to support ‘a small, statistically significant relationship’ in the normal range of birthweights, although the authors note that this may have been due to publication bias, selection bias or residual confounding. Further, included studies were limited to those from the USA and UK. Since this review, other studies in non-Western countries seem to support these findings, and it has also been suggested that there may be effect modification in this association across different levels of family socioeconomic status. The question remains whether the observed associations are indeed causal, which would support the hypothesis that intrauterine growth (represented by birthweight) is the mechanism, or whether pre- or postnatal maternal/familial factors may be relatively more important.

**Intrauterine environment: a plausible hypothesis with weak evidence**

There is an ongoing debate favouring either intrauterine (of which birthweight is a key marker of maternal-fetal interaction during pregnancy) or extra-uterine (measured by child growth and/or socioeconomic factors) explanations as the dominant influence on cognitive development and mental performance in children and across the life course. Support for the former has come from early studies suggesting suboptimal intrauterine growth may affect brain and cognitive development. On the other hand, evidence from the Dutch Hunger Winter studies (a ‘natural experiment’ which arose due to the embargo of food to occupied regions of Holland in 1944–45) has suggested that starvation conditions during pregnancy, although influencing the birthweight of children, had ‘no detectable effects on the adult mental performance of surviving male offspring’. Difficulties arise in this literature due to the various study designs employed, methods and timing of exposure and outcome assessment including cognitive ability, growth in children and childhood socioeconomic circumstances. This has implications in both determining the relative importance of intra- vs extra-uterine environment and at what point to carry out potential interventions, whether in utero or during the early (or later) postnatal period. The field is in dire need of improvements in study and analytical designs which will help strengthen causal inferences and help translate results of future studies into clinical practice.

Interpreting associations between birthweight and later outcomes requires reflection on what birthweight can be taken to represent. The notion of birthweight as a unitary exposure is clearly problematic; as David Haig points out ‘A gram of fat is not interchangeable with a gram of bone, nor with a gram of lead. Birthweight is the final outcome of many factors, only some of which may be related to risk’. No one would support the notion that raising birthweight by whatever means would be beneficial. At best, birthweight serves as a proxy that may allow us to understand modifiable processes that could be targets for intervention. However, in many domains even this aspiration can be seen to be problematic. The oft-studied association between birthweight and infant mortality is a case in point. As Jacob Yerushalmy demonstrated 50 years ago, the curves relating birthweight to infant mortality differ between offspring of smokers and non-smokers, so that at any given birthweight offspring of smoking mothers had lower mortality; a somewhat counterintuitive finding. This ‘birthweight paradox’ has generated much discussion and analysis, which at the very least demonstrates that any straightforward causal interpretations of birthweight and later outcome associations are untenable.

**Need for creative analytical strategies**

Even without the particular issues around interpreting the meaning of birthweight associations, the problem of causal inference in studies relating intra- or extra-uterine influences on later outcomes (which is general to the whole of epidemiology) is considerable. Despite such difficulties, there are novel analytic strategies which can be employed to strengthen causal inferences in this field. We discuss four such strategies that hold some potential for providing us insights into ascertaining the relative importance of intrauterine influences on child outcomes.

One such strategy is to compare and contrast maternal and paternal exposures with offspring outcomes. In order to assess the plausibility of a direct biological link between intrauterine exposure and child cognitive development, the effects on offspring outcomes should be much stronger for maternal exposures such as smoking, diet, alcohol use or body mass index than for the same exposures measured among fathers. Demonstration of a stronger effect for maternal exposures would imply that such associations are causal, whereas effects similar in magnitude in relation to paternal exposures would suggest that associations may have arisen through social, environmental or genetic influences acting at the family level.

A second approach is to explore how the proposed associations are related to the timing of exposure. For example, an exposure which occurs during pregnancy would be expected to have a different effect compared with exposures before or after pregnancy if a specific intrauterine influence were present. In the case of the
Dutch Hunger Winter studies, it was possible to work out a relatively accurate estimate of the timing of nutrition deprivation by examining the conditions 9 months prior to birth for cohorts born in the famine regions. With other exposures, it may not be feasible to observe the timing with a great degree of accuracy as they change little before, during and after pregnancy.

A third is sibling approaches, which have also been used to strengthen causal inferences for intrauterine exposures. In such studies, the focus is on siblings from the same mothers who differ with respect to their exposure. A fixed-effects approach can be used in such studies to account for both observed and unobserved covariates at the mother (family) level in order to obtain a causal effect for the exposure-outcome relationship. Such approaches have limitations, however, which require consideration.

Finally, both genetic (‘mendelian randomization’) and non-genetic instrumental variables approaches can be useful in estimating causal associations. In such approaches, an instrumental variable is identified which is only related to exposure and not related to confounding factors, or the outcome of interest is utilized to correctly model the joint associations to arrive at a causal effect. Such approaches have been used to explore the intrauterine influence of maternal smoking on birthweight, both with non-genetic and genetic instruments.

Concluding remarks

In summary, although empirical studies such as the one by Huang et al. from diverse contextual settings can strengthen the evidence base, there is a need for more creative analytical strategies to truly ascertain the relative importance of intrauterine versus extrauterine influences on childhood cognitive outcomes and more generally on other health outcomes.

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