Commentary: One-carbon metabolism has major implications for fetal growth and development beyond neural tube defects

Sarah J Lewis
School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN, UK. E-mail: S.J.Lewis@bristol.ac.uk

Small effect sizes may not be headline grabbing but can nonetheless have important public health implications. The paper by Yajnik et al.\(^1\) in the current issue of IJE reports on a 56-g reduction in birthweight of infants per standard deviation (SD) increase in homocysteine levels during pregnancy. However, a comparison of women in the lowest vs highest quartile for homocysteine suggests the potential for much greater effects (differences of 110–150 g). In addition, somewhat unusually, the estimates of the effect of maternal homocysteine on birthweight using a genetic proxy in the study by Yajnik and colleagues show a much stronger association (a reduction of about 250 g per SD of homocysteine) than the observational biomarker-birthweight association. This implies that the ‘real’ effect of one-carbon metabolism and its related nutrients (in the absence of confounding by other factors) is much greater than the 50 g reported, and is even greater that the difference in birthweight of offspring from smoking and non-smoking mothers (around 150 g to 200 g difference)\(^2\) and suggests a key role of this pathway in fetal growth and development.

The use of Mendelian randomization to identify causal risk factors for adverse fetal outcomes

Adequate nutrition and a ‘healthy lifestyle’ are known to be important for fetal and maternal health during pregnancy but, due to confounding, the role played by specific nutrients is somewhat elusive despite thousands of studies on the subject. Mendelian randomization was first suggested in this journal in 2003\(^3\) as a principle which can avoid confounding by using genetic variants as surrogates for differential exposure levels. This approach has been extended by using maternal genotypes as indicators of in utero environment and has previously also shown that elevated maternal glucose levels during pregnancy leads to offspring with a lower birthweight\(^4\) and has been used as a proof of principle, to add further weight to the evidence that smoking reduces fetal birthweight.\(^2\) In addition, maternal MTHFR C677T genotype has been found to be associated with neural tube defects (NTD) in offspring,\(^5\) supporting the randomized controlled trial evidence that folate is a risk factor for NTDs.

The instrumental variable analysis calculates the unconfounded effect of the exposure on outcome given the effect of the genetic variant on exposure and the effect of the genetic variant on outcome. The instrumental variable analysis by Yajnik et al.\(^1\) shows a larger effect than the observed homocysteine-birthweight effect, which suggests that the observed analysis is an underestimate.

Gene-environment interaction shows real importance of pathway

Although maternal MTHFR C677T genotype has been used as a surrogate for circulating homocysteine levels in the study by Yajnik et al.,\(^1\) the evidence suggests that actually what may be important is the interaction between maternal genotype and circulating folate levels. The effect of being in the lowest vs the highest quartile for red cell folate concentration was a reduction in birthweight of 561 g among those with TT genotype: a finding which is in accordance with a study by Jacques et al.\(^6\) who showed that the effect of genotype was far greater among those with low plasma folate.\(^5\)
In addition, a similar gene-environment interaction was observed for birthweight in a very different population in Newcastle, UK, in 2005. These findings collectively suggest a much more important role of this pathway in birthweight than first glance would indicate.

**Birthweight as a surrogate outcome**

Birthweight is nearly always recorded for infants, even in less developed countries, and it is a good surrogate for growth during gestation. Barker used associations between birthweight and later adult coronary heart disease to postulate the fetal origins of disease hypothesis. However, it is unlikely that low birthweight causes coronary heart disease in adulthood; it is more likely that the same mechanisms which affect growth in the fetus lead to other perturbations which affect later disease risk. We know this because observations from the Dutch Hunger Winter show that women exposed to famine during mid to late gestation had babies with significantly reduced birthweights, in contrast to those exposed in the first trimester whose birthweight were unaffected. Despite this, children affected by famine in the first trimester still went on to have higher rates of heart disease than the control population who were not exposed to famine.

**A pointer towards epigenetic programming**

In addition to affecting birthweight, the MTHFR C677T genotype is thought to have wide-ranging effects: from neural tube defects and miscarriage, to vascular disease, cancer, depression and schizophrenia. How can it be the case that a common genetic variant can have such wide-ranging effects? The answer is that the one-carbon pathway is key to two vital cellular processes, DNA synthesis and repair, and DNA methylation. The MTHFR enzyme is important in regulating this pathway and directing folate metabolites between the two processes. Methylation of DNA is an important (if not the most important) mechanism controlling gene expression. Epigenetic marks such as DNA methylation which control gene expression are largely determined in utero and can be lifelong and far reaching. Friso et al. assessed genomic DNA methylation levels in peripheral blood mononuclear cell DNA from 105 subjects who had the MTHFR TT genotype and 187 with the MTHFR CC genotype. They found dramatic (50%) reductions in global methylation levels in those with the TT genotype, but only among those with low folate.

**Conclusion**

The findings by Yajnik et al. add to a growing body of evidence which points towards a key role of the one-carbon pathway in determining birthweight, with folate being particularly important among those with the TT genotype. Since birthweight may only be a proxy for ‘fitness’ at birth, it is likely that the effects of folate/homocysteine are much more far reaching. In addition, this adds more weight to the evidence that DNA methylation is the mechanism by which nutrition during pregnancy affects offspring growth and also later disease risk.

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**References**