Commentary: Type 2 diabetes and birth weight—genetic and environmental effects

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Type 2 diabetes is one of the archetypal common complex diseases. Its prevalence is rising leading to increasing morbidity and mortality. A genetic contribution to type 2 diabetes has been suggested and sought eagerly for some time. Environmental influences are well described—notably effects of diet and exercise—and underpin recent increases in prevalence. In addition, type 2 diabetes is one of the chronic conditions most clearly associated with potential in utero or early life programming. Such early environmental influences have been proposed both in the context of low birth weight and maternal diabetes. There is a huge challenge in unpicking the various environmental and genetic effects not least as the influence of such factors might be different at different times in the life course—most obviously in the proposed role of the early environment. Nevertheless, it is hoped that this understanding will deliver the prize of increased understanding of the aetiology of type 2 diabetes with the expected dividend of improved prevention and treatment of diabetes.

Bergvall et al. have examined a very large twin cohort using the Children of twins approach to attempt to discern genetic and environmental contributions to type 2 diabetes. There are a number of interesting observations. First, they confirm the previously observed association of paternal diabetes to lower birth weight in their offspring. Conversely, maternal type 2 diabetes was associated with increased offspring birth weight—most likely secondary to environmental effects of maternal diabetes. Furthermore, they demonstrate that in analysis of the birth weights of twins and their offspring—including both mono and dizygotic twins—the association between parental and offspring birth weight was largely explained by genetic factors. Taken together their findings would appear to support the contention that the association of birth weight and type 2 diabetes risk may well be reflecting pleiotropic genetic effects. Ultimately, however, even in this very large data set Bergvall et al. were not able to be entirely conclusive about the genetic and environmental contribution to the association of birth weight and later diabetes. Happily, help may be on the way. This year has also seen an unprecedented increase in our knowledge of the genetics of type 2 diabetes. Several groups—usually based on very large international collaborations have supplied a number of replicated genetic associations—contributing up to seven genes which appear to contribute to type 2 diabetes risk.
along with others contributing to risk of obesity. Most excitingly many of these new associations are in largely uninvestigated genes—suggesting that entirely new areas of cell biology will impact of diabetes risk. Investigation of the role of this genetic variation on birth weight is already well under way. Furthermore, the last 10 years has seen major developments in our knowledge of monogenic diabetes—predominantly Maturity Onset Diabetes of the Young (MODY). Investigation of the genetic causes of MODY provided proof of concept for pleiotropic effects of diabetes causing polymorphisms influencing both diabetes risk and birth weight. The situation is complex, however. Such variation when present in mothers may increase birth weight by causing maternal hyperglycaemia. At the level of the fetus, mutation in the glucokinase gene is associated with reduction in birth weight due to reduction in insulin secretion. More recently, separate MODY mutations have—when effects of maternal hyperglycaemia are excluded—been shown to result in either no change (HNF1A mutation) or an increase (HNF4A mutation) in birth weight. This unexpected increase in birth weight in those carrying HNF4A mutation likely reflects early paradoxical increases in insulin secretion in utero. It is possible then that the effect of common genetic variation predisposing to type 2 diabetes will be similarly heterogeneous in their effects on birth weight.

It is expected that these diverse investigations will also have impact upon large scale epidemiology such as that carried out by Bergvall et al. As parts of the jigsaw puzzle of diabetes causation are put in place, this can be used to find to solve other parts of the question of how diabetes risk and early development might be interlinked.

References