**////Title: Do Maternal Influences on Birthweight Influence Future Cardiometabolic Risk?**

**////Stand-first**: Adverse environmental factors in the mother’s womb and/or during the first years of life have traditionally been thought to be responsible for an increased risk of cardiometabolic disease for children later in life. Dr Gunn-Helen Moen [MO-en] at the University of Oslo in Norway and her collaborators used sophisticated statistical and genetic techniques to identify whether there is a causal effect of environmental factors that influence intrauterine growth on future cardiometabolic risk in the child. Their results were surprising but important.

**////Body text:**

There is a well-documented relationship between having a lower weight at birth and having an increased risk of developing cardiometabolic diseases – such as cardiovascular disease and type 2 diabetes – later in life.

The Developmental Origins of Health and Disease hypothesis proposes that adverse environmental factors (such as undernutrition) in the womb or poor nutrition during the first years of life increase the risk of a child developing cardiometabolic disease in the future. However, evidence supporting this hypothesis has primarily been gathered from observational or animal studies, meaning that it is unclear whether the observational association represents a causal relationship.

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Mendelian [men-dee-LEE-uhn] randomisation is an epidemiological method that can be used to investigate whether an observational association between an exposure and an outcome truly represents a causal relationship. The basic idea is that, if an exposure (such as low birthweight) causes an outcome (such as cardiometabolic disease), then genetic variants that are associated with the exposure, should also be associated with the outcome. The reason for examining genetic relationships like these, rather than studying the exposure and outcome directly, is that genetic variants are less susceptible to many of the problems of traditional observational epidemiology (like confounding and reverse causality), and so associations are more likely to reflect causal relationships.

Nevertheless, previous studies that had attempted to use the Mendelian randomisation approach to look at the relationship between lower birthweight and cardiometabolic disease, had only examined the relationship between offspring genetics, birthweight and cardiometabolic disease. This failure to take into account the potential influence of maternal genetics on the intrauterine environment leads to difficulty interpreting the results. In other words, it is important to consider both maternal and offspring genotype in these Mendelian randomisation studies when trying to assess the importance of the intrauterine environment on future cardiometabolic risk.

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Dr Gunn-Helen Moen at the University of Oslo in Norway, carried out an important study utilising this approach in collaboration with other international researchers to better understand how maternal influences on birthweight affect future cardiometabolic risk.

Dr Moen and her colleagues used data from 26,057 genotyped mother-child pairs from the Norwegian Nord-Trøndelag [TRON-de-lag] Health (also known as the HUNT) study to explore the proposed Developmental Origins of Health and Disease hypothesis mechanisms related to foetal growth and lower birthweight for a range of cardiometabolic risk factors.

More specifically, Dr Moen and her colleagues investigated whether a genetic risk score of maternal genetic variants known to be associated with child birthweight was also associated with subsequent cardiometabolic risk factors (such as blood pressure and body mass index) after statistically controlling for the effect of the offspring genome. Similar analyses were performed in 19,792 father-child pairs to ascertain whether there was also evidence for a postnatal environmental effect (such as that arising from the impact of parental nature) of the parental genetic risk score on cardiometabolic risk.

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Dr Moen and her colleagues found little evidence for a maternal (or paternal) effect of birthweight associated genetic variants on offspring cardiometabolic risk factors after controlling for the offspring genome.

They argue that this finding shows that any potential effect of intrauterine growth on future cardiometabolic disease risk is likely to be small compared to the effect of other risk factors.

However, the researchers did show that many of an individual’s own genetic variants that were related to low birthweight, were also associated with an adverse cardiometabolic risk profile in later life. This finding suggests that the robust relationship between low birthweight and increased cardiometabolic risk is likely to be driven by an individual’s own genome, rather than environmental factors.

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The HUNT study is one of the largest population cohorts in the world containing genotyped mother-child and father-child pairs along with records of child birthweights. The large size of this study means that it is statistically powerful enough to enable researchers to draw meaningful conclusions from the data.

Another advantage is that the average age of the HUNT study child is approximately 40 years old, which means that some individuals have already developed observable signs of cardiometabolic disease.

Nonetheless, Dr Moen and her colleagues note that there are also some limitations of the study. For example, it is assumed that the maternal genetic variations that affect child birthweight do so via foetal growth but it may not be foetal growth/birthweight itself that is relevant for the validity of the Developmental Origins of Health and Disease hypothesis. Rather, it is possible that other early life environmental factors that don’t affect offspring birthweight are important and have negative effects on an individual’s future risk of cardiometabolic disease.

Furthermore, the Mendelian randomisation method typically tests small changes in an exposure. However, it may be that the Developmental Origins of Health and Disease mechanisms that are important in the genesis of cardiometabolic risk are only relevant in the case of extreme environmental effects like famine or disease, which may qualitatively differ from smaller perturbations that produce more subtle variations seen in a relatively healthy population.

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Overall, Dr Moen and her colleagues conclude that there was no strong evidence for a causal effect of the maternal intrauterine environment causing lower birthweight on cardiometabolic risk factors in this study. They argue that environmental factors that influence intrauterine growth are unlikely to be a major determinant of adverse cardiometabolic outcomes and the risk of going on to develop conditions like cardiovascular disease and type 2 diabetes appears to be driven more significantly by the genetics of each child.

While inconsistent with initial predictions, these are surprising but important findings. Dr Moen and her colleagues emphasise that their research only tested one aspect of the Developmental Origins of Health and Disease hypothesis, and that there are other possible mechanisms of action that are worthy of future examination.

This SciPod is a summary of the paper ‘Mendelian randomization study of maternal influences on birthweight and future cardiometabolic risk in the HUNT cohort’, published in Nature Communications. DOI: <https://doi.org/10.1038/s41467-020-19257-z>

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