Birthweight phenotype genotype mismatch in cardiometabolic programming

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Background: The Barker hypothesis, that poor fetal growth can program adult cardiometabolic disease, has been contradicted by genetic investigations that demonstrate direct pleiotropic effects from birthweight genetics on cardiometabolic risk. We investigated whether the cardiometabolic effects of birthweight genetics depended on the offspring's birthweight phenotype.

Methods: Repeated measures of adult body mass index, insulin resistance, low-density lipoprotein cholesterol and systolic blood pressure were modelled in a cohort of 1167 offspring followed from mid-pregnancy through to age 27. In linear mixed-effects models, we tested the associations of birthweight polygenic scores in the presence of a high vs low birthweight phenotype.

Results: Here, we show that a birthweight phenotype-genotype mismatch is associated with central adiposity and insulin resistance in young adults. In fetuses that fail to reach their growth potential (i.e. low phenotypic birthweight with high birthweight polygenic score), we find increased central adiposity and insulin resistance. In those that exceed their growth potential (high phenotypic birthweight with low birthweight polygenic score), data suggest increased insulin resistance. We find no evidence of phenotype-genotype mismatch influence on low-density lipoprotein cholesterol and systolic blood pressure.

Conclusion: These data support the Barker hypothesis, and we suggest that it is the deviation from fetal growth potential, rather than crude BW, that underpins the relationship with adult disease risk. Identification of individuals with a birthweight phenotype-genotype mismatch could allow early identification of children at future risk.