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Published by Oxford University Press on behalf of the International Epidemiological Association *International Journal of Epidemiology* 2010;**39**:1276–1278

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doi:10.1093/ije/dyq109

Commentary: What can evidence on intergenerational transmission of risk of low birth weight and cardiovascular disease tell us about mechanisms?

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Accepted 18 May 2010

The potential relevance of establishing an association between a child's birth weight and their parents' and grandparents' cardiovascular disease risk

The paper by Manor and Koupil¹ seeks to determine whether the known link between an infant's birth weight and the mother's risk of cardiovascular disease² extends to the grandparent's generation. This possibility has had little investigation to date.

The paper builds on evidence that an infant's birth weight is associated with its future risk of Cardiovascular Disease (CVD), hypothesized to be due to metabolic dysfunction occasioned by poor fetal growth.³ One of the major determinant's of

infant birth weight is the mother's size, which in turn is related to her own birth weight.⁴ The association between birth weight in the infant and both the mother's birth weight and CVD risk is, therefore, not surprising. However, there are several potential causal pathways that could underpin this joint risk of low birth weight in the infant and high CVD risk in the mother which the examination of grandparental associations could help unveil. These explanations include the following.

- (1) A mother who is small from any cause, environmental or genetic, might influence the size of her offspring directly through physiological and anatomical pathways. These pathways might include placental factors and pelvic dimensions.^{5,6} If small birth weight alone increased risk of CVD, then under this scenario CVD risk would be high in both mother and any offspring.

- (2) Alternatively, the mother might carry genes that jointly influence the risk of low birth weight and CVD risk.² These could be inherited from either her mother or father—or both. They could be found in genomic DNA or mitochondrial DNA.
- (3) A third possibility is that shared environmental factors in each generation could be responsible for both low birth weight and high CVD risk in each generation.

While the type of data presented here on apparent intergenerational transmission of risk cannot conclusively separate these possibilities, it can help identify which of the possible pathways is likely to hold the explanation.

If (1) was correct, an association between mother's CVD risk and the infant's birth weight would be expected, but the association would be attenuated in the grandmother. This is because low birth weight is only partly explained by the mother's size, and even less so by grandmother's size or birth weight.⁴ As father's size does not seem to influence birth weight in a major way,⁴ little association with CVD in the father via the birth weight pathway would be anticipated.

If the explanation lay in the pathway described in (2), the associations would vary depending on whether genomic or mitochondrial genes were involved. With the former, associations would be anticipated between the proband's birth weight and both parental and grandparental CVD risk, but decreasing with each generational distance from the proband.

If mitochondrial genes were involved, there would be no association with male CVD risk in each generation, but there would be an association with risk in both mothers and grandmothers, which would be of similar strength.

The associations expected if (3) applied would depend on the extent to which a particular hypothesized environmental cause was transmitted from one generation to the next. Smoking is an obvious potential environmental explanatory factor.⁷ Population trends indicated that the parent's generation in this cohort were less likely to smoke than the grandparent's generation; if maternal smoking was responsible for the lower birth weights of the children in this study and her smoking was correlated with maternal grandparent's smoking, one might anticipate that the CVD risk in grandparents might be higher than that in the parents.

Findings from the Uppsala Study

The data reported in this paper come from the Uppsala Birth Cohort Study, which involved a sample of 28 175 infants, 14 129 mothers, 13 863 fathers and close to 4000 grandmothers and a similar number of grandfathers.

The central findings are that risk of all-cause mortality in mothers was inversely related to infant's birth weight, with an Odds Ratio (OR), of 1.82 (95% CI: 1.07–3.11) in the mothers of babies in the lowest 5% of birth weights compared with mothers of babies with birth weights within the inter-quartile range. The association was even stronger for CVD—with an OR of 2.68 (1.08–6.64) for mothers of those infants in the lowest 5% of birth weights. There was no association between infant's birth weight and father's risk of either of these two outcomes.

The authors go to considerable lengths to demonstrate associations among grandparents. However, the only estimates of association using the continuous data for birth weight where there was some evidence of an association are those for all-cause and CVD mortality for maternal grandfathers. Even then, the ORs for the lowest birth weight category are modest: 1.24 (1.04–1.49) and 1.31 (1.01–1.45) for all cause and CVD mortality, respectively.

The authors then separate the data into two time periods—pre- and post-1977. They note that, in a quadratic model, an association for CVD mortality with birth weight is evident in maternal grandmothers of probands born before 1977. However, the test for heterogeneity of the association between the time periods indicates that this separate analysis is not justified.

So, the only convincing finding is that mother's all-cause and CVD mortality, in particular, is related to her infant's birth size. The most plausible interpretation of the data on the grandparental associations is that they are weak or non-existent, since the 95% confidence intervals are sufficiently narrow to exclude material effects.

What inferences should therefore be drawn about the hypothesized causal pathways? Based on the data from this study, the most plausible inference is that physiological or anatomical restrictions imposed on a developing fetus by the mother's small size—whatever the cause—is the pathway through which the joint risk of low birth weight and future risk of CVD are primarily transmitted. The results of this study do little to support a common genetic cause of both outcomes, nor do they suggest that environmental factors shared between grandparents and parents are a substantial contributor.

The three-generation evidence presented by Manor from the Uppsala Cohort supports inferences drawn from previous studies of two generations that the relevant aetiological process involves the mother. In addition, this study, by providing the opportunity to examine the association in maternal grandmothers as well as mothers, permits us to exclude the possibility that mitochondrial genes may underlie the associations observed. A note of caution here is that a recent record linkage study in Scotland did demonstrate an association between both maternal and

paternal grandparents' CVD risk and grandchild's birth weight.⁸

Funding

O.C.U. postdoctoral position is funded by Australian National Health & Medical Research Council (NHMRC). Population Health Capacity Building (Grant 436914).

Conflict of interest: None declared.

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