Smoking, birthweight, and mortality across generations

Rachel Huxley

Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 1300 S 2nd St, Suite 300, Minneapolis, MN 55454, USA

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This editorial refers to ‘Cardiovascular mortality in relation to birth weight of children and grandchildren in 500 000 Norwegian families’, by O. Naess et al., on page 3427

Beginning in the 1980s there has been considerable research into the possible role that the intrauterine environment may have in ‘programming’ adult disease—in particular, cardiovascular diseases (CVDs) and diabetes—in later life. The original ‘foetal-origins’ hypothesis was developed by David Barker and colleagues at the University of Southampton who produced a substantial number of reports detailing the possible effects that poor maternal and foetal nutrition (as measured most often by birthweight) had on cardiovascular risk factors and mortality in later life. This ‘foetal-programming’ was suggested to be an adaptive response made by the fetus in order to survive a suboptimal ‘intrauterine’ environment whilst simultaneously rendering the same individual at greater risk of chronic disease in adulthood. Andrew Hattersley and colleagues subsequently proposed an alternative explanation. They suggested that genetic factors were primarily responsible for both foetal growth restriction and the development of insulin resistance and other cardiovascular disorders in adult life, the ‘foetal-insulin’ hypothesis. However, trying to disentangle any genetic effects—‘nature’—from the impact of the maternal and foetal environment—‘nurture’—on the associations between birthweight and disease in adult life is a challenging undertaking.

Naess and colleagues have now explored the relationships between offspring birthweight and CVD mortality in both parents and grandparents among half a million Norwegian families. By doing so, they hoped to elucidate the potential pathways—nature, nurture, or a combination thereof—that mediate the reported associations between low birthweight and CVD mortality in previous generations. Their hypothesis was that if the associations between birthweight and CVD mortality were similar in all four grandparents, then this would provide evidence of some underlying genetic cause.

In this study, the authors have examined mortality rates from major causes of death among the grandparents and parents of offspring born in Norway between 1960 and 2008. The main findings from this study showed that parental mortality from CVD decreased across successive quintiles. The magnitude of effect was equivalent to a 15% reduction in risk of CVD mortality per quintile in mothers compared with 5% in fathers, results consistent with those from a previous meta-analysis. Whilst these data are consistent with genomic influences, the authors were unable to exclude the most obvious environmental cause of the association, that of parental smoking (due to an insufficient number of parental deaths since information on maternal smoking habits was collected only after 1997). Given the strong inverse associations between maternal smoking and offspring’s birthweight (the difference between smoking and non-smoking mothers in the Norwegian population has been estimated to be 197 g5) and between offspring’s birthweight and parental mortality from smoking-related disease (i.e. lung cancer and chronic obstructive pulmonary disease), it therefore stands to reason that maternal (and to a lesser extent, paternal) smoking was largely driving the observed association between offspring birthweight and parental mortality.

In the subpopulation for whom information on maternal smoking habits was available, maternal smoking was strongly associated with birthweight; 27% of offspring born in the lowest quintile of birthweight had mothers who smoked in pregnancy compared with 15% in those born in the highest quintile. Moreover, it is likely that an even higher number of the mothers who smoked as they would have been among the first generation of women where smoking was popular and who would also have been largely ignorant of the adverse health effects of smoking [in contrast, relatively few of the grandmothers would have smoked; (Figure 1)]. In support of this hypothesis, a previous retrospective study of 35 000 Norwegian women who gave birth between 1970 and 1991 estimated the prevalence of smoking in pregnancy to be 32% in 1970. Even if the mother (and grandmother) did not smoke, it is likely, given the high rates of smoking among fathers (and grandfathers; Figure 1), that she would have been exposed to second-hand smoke from a smoking spouse—which also impacts negatively on birthweight.

* Corresponding author. Tel: +1 952 250 1730, Fax: +1 612 624 0315, Email: rhuxley@umn.edu

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Further evidence to suggest that confounding by shared environmental factors such as parental smoking and low socio-economic position is probably more important than genetic effects in mediating the relationship between offspring birthweight and parental mortality is the lack of specificity of the association. Although not reported here, previous studies have shown associations between birthweight and outcomes that are known to be associated with low socio-economic position (such as accidents and violence) of a magnitude greater than those observed for CVD.

In the study of Naess et al., there were much weaker inverse associations among the grandparents between the offspring’s birthweight and mortality from all causes and from CVD. However, after adjustment for maternal smoking, the relationships between offspring birthweight and grandparental CVD mortality were largely attenuated, suggesting that maternal smoking (and other associated health behaviours), more so than common genetic factors, was the key underlying mechanism mediating the relationship between offspring birthweight and intergenerational mortality. It would have been informative, if the numbers had allowed, if the authors had performed an additional analysis restricted to non-smoking mothers of high socio-economic position, to confirm further the confounding effect of maternal smoking and low socio-economic position.

A possible exception to this was diabetes—which is a less valid endpoint that CVD; for both mothers and maternal grandmothers, the relationship to offspring’s birthweight was U-shaped, with the greatest risk of diabetes-related mortality most evident in those whose offspring were born in the highest quintile of birthweight. For fathers, and for parental grandfathers, there was evidence of an inverse association. These opposing relationships suggest that the relationship between birthweight and diabetes mortality is influenced by a combination of intrauterine and genetic effects. Maternal factors such as diabetes and obesity in pregnancy are associated with larger offspring as well as increased maternal risk of developing diabetes in later life, whereas elevated risk of paternal and paternal grandfather mortality in those with offspring in the lowest quintile of birthweight is consistent with genomic influences. These findings are intriguing, but remain speculative; future studies that have more detailed information on behaviour and lifestyle risk factors in both parents and grandparents are required in order to clarify more fully the role of genetics and the environment on the relationship between birthweight and intergenerational mortality.

Almost in passing, what the study by Davey Smith and colleagues so effectively demonstrates is the detrimental intergenerational effect that parental smoking has—particularly among mothers. Smoking remains the leading preventable cause of death in countries such as the UK and the USA despite declines in the prevalence of smoking in the last couple of decades. It is also a major cause of infant morbidity and mortality and is estimated to be responsible for 30% of small for gestational age infants and 5% of infant deaths. Parental smoking also increases the likelihood of the child taking up the habit, thereby propagating the vicious cycle. Despite the high level of awareness of the hazards of smoking, an estimated 13% of women in the USA continue to smoke during pregnancy far above the 1% objective set by the ‘Healthy People 2010’ campaign.

In summary, the influence of any genetic effects on the relationship between birthweight and parental and grandparental CVD mortality is likely to be small and far outweighed by the impact of smoking and associated parental behaviours—particularly of the mother, during pregnancy.

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