Editorial

What is it about boys?

From parent to child

Cornerstones of modern day epidemiology include both life course epidemiology and the field of developmental origins of adult disease, where considerable focus is placed upon parental (largely maternal) influences on offspring health and development. Similarly, the ascendency of genetic epidemiology shines a spotlight on heritable traits passed from parents to offspring. A recent addition to the discussion of intergenerational influences on long-term health has been the contribution of epigenetic processes. Epigenetic mechanisms, present as persistent but malleable marks on the genome and as regulators of gene expression, are prime candidates to be the biological mechanism underlying the lasting impact of early life exposures on long-term health. Less widely acknowledged is that the relationship between parents and children is not unidirectional and that children can affect the health of their parents.

And child to parent

In evolutionary terms, reproduction imposes fitness costs and reduces parental survival across many species, including humans. Historically however, children have endowed an economic benefit on their parents, although in modern society children often represent an economic burden to their parents—while also being emotional and social assets. The relative biological and sociocultural influences on survival are difficult to disentangle. Several studies have considered the long-term benefits or detriments of having children, generally (but not universally) concluding that having sons compromises maternal mortality whereas daughters have no such apparent influence.

Should sons come with a health warning?

As a mother of two sons, it comes as no surprise to me to hear that raising sons may be detrimental to my health. Studies of a Scandinavian nomadic population have reported decreased longevity in mothers (0.65 years) for each son raised to adulthood but increased maternal longevity (0.66 years) for each daughter. These intriguing observations, although not consistently replicated, have elicited various explanations—from the increased physiological demand of sons during gestation (sons grow more rapidly in utero and have a higher birthweight than daughters) to sociocultural influences in later life, where daughters are more consistent caregivers. More anecdotally, and speaking from personal experience, reduced longevity could be attributable to anything from chronic exposure to detergent required to sanitize a household of boys, periodic infection from sub-zero spectating of winter sporting fixtures or musculoskeletal demise from constantly picking clothes up from the ‘floorrobe’; familiarization with this term I attribute to Finbar J Rhodes (age 11 years, Boston, MA, USA), to describe the storage of the contents of his wardrobe on his bedroom floor.

The largest study of the influence of offspring sex on parental mortality undertaken to date, using over 33,000 couples from the Utah Population Database, reported a small but adverse effect of having sons on maternal mortality. The effect was not observed in fathers, suggesting that the influence of sons on parental mortality is less likely to be via a sociocultural (or a shared environmental) route and more likely to be explained by a biological phenomenon. Alternatively, boys may simply be more demanding than girls, specifically for mothers, as anecdotally noted above. Nevertheless, various explanations have been posited with regard to possible biological mechanisms, in addition to the excess physiological cost of bearing sons mentioned earlier, and other mechanisms maybe important but as yet unrecognized.

A role for epigenetics?

Recent developments in the field of epigenetics have suggested that the regulation of gene activity through epigenetic alterations may occur as a result of environmental exposures including social stress, raising the possibility that child behaviour might impact upon the epigenome of
the parent. The dynamic properties of the epigenome across the life course have been well documented, adding plausibility to this idea.

**A biological explanation: microchimerism and mortality**

Fetal microchimerism, the existence of cells transferred across the placenta from fetus to mother during pregnancy, is believed to influence disease risk in adult women. Genomic technologies allow the detection of male fetal DNA (the Y chromosome) at very low levels in peripheral blood samples drawn from women (female fetal DNA is much less easy to distinguish from that of the mother). This sensitive and specific analysis can thus confirm the presence of male cells, but what exactly can this tell us about the importance of this phenomenon in terms of long-term maternal health?

The authors of a paper in this issue of the *International Journal of Epidemiology* report an association between male microchimerism in women aged 50–64 years and subsequent survival. A 60% lower all-cause mortality was observed among male microchimerism-positive women compared with negative women. This finding however conflicts with previous literature but, taken collectively, agrees in favour of a detrimental effect of bearing sons. Nevertheless, the thinly populated field requires both additional large-scale observational studies as well as the pursuit of approaches to investigate potential mechanisms to explain this tentative relationship between offspring sex and maternal longevity and all-cause mortality, and analysis of fetal microchimerism may offer one such route.

Perhaps the focus on male microchimerism is misplaced; no solid conclusion can be drawn as to whether the observed effect is sex specific, given that no data are available on female microchimerism. It is biologically plausible that any microchimerism may impact upon maternal health. Do we make inferences about male microchimerism purely because we can detect Y chromosome DNA? Is female microchimerism as widespread and as apparently protective as male microchimerism, or could it have detrimental effects? These questions remain to be addressed.

Microchimerism might only be expected to occur in women via the maternal:fetal interface, although this could be following either a viable pregnancy or a spontaneous (possibly very early) or induced abortion. Other routes are plausible, such as via blood transfusion. Kamper–Jorgenson et al. previously reported that only 82.3% of women in this study population, who were male microchimerism-positive, had reported giving birth to a live-born son. Indeed, previous studies have shown male microchimerism to be not infrequent in women without live-born sons. Over two-thirds (70%) of women showed evidence of male microchimerism in the most recent study, suggesting that this number had carried a male fetus for at least part of a pregnancy. Comparison of male microchimerism-positive women with and without sons (or children) could be an informative approach to dissecting the true biological effects of microchimerism itself, as this would remove the potentially confounding influences of sociocultural factors in ‘raising’ sons (or children) which are implicit in observational data and that may impact upon maternal mortality.

Measurement of fetal DNA in the maternal circulation, the analysis of its association with health outcomes, and inferences that may be drawn from this have parallels with many other molecular biomarkers, including telomere length and epigenetic signatures that are studied in a bid to illuminate the biological pathway leading to compromised longevity. It is often extremely challenging to delineate cause from a potential bystander phenomenon, particularly when the molecular pathways involved are not known in detail. It remains to be established whether fetal microchimerism has value as a robust predictive biomarker of maternal all-cause mortality, whether it is causally related to this outcome and, if so, whether intervention to manipulate levels of microchimeric cells might have some future health benefit.

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In summary, it would appear that sons pose some health risks for their mothers but not their fathers, despite the economic benefits they may afford in later life. The relative contribution of sociocultural and biological factors is unclear and, if biological, the mechanisms remain to be established. In the meantime I shall encourage my sons to pay special attention to nurturing their mother in an effort to compensate for any possible detrimental effect that may exist!

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