

# **Pregnancy and the risk of cardiovascular disease: is the relationship due to childbearing or childrearing?**

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**Pregnancy has long been considered as a risk factor for cardiovascular disease. However, recent evidence showing similar relationships between the number of children and cardiovascular disease in men suggests that childrearing is more likely than childbearing to affect the risk of CVD.**

A major problem in the prevention of cardiovascular disease (CVD) is the difficulty in identifying individuals at high risk at an early enough stage for them to benefit from lifestyle modification or preventive medications. This is especially the case for women, whom, on average, develop CVD some 5 to 10 years later than men. Pregnancy is a factor unique to women and it is now largely recognized that pregnancy complications, such as pre-eclampsia and diabetes are risk factors for the development of CVD or diabetes decades later.<sup>1</sup> Furthermore, it has been suggested that the number of pregnancies or live births is associated with the risk of CVD later in life. If causal, more intensive screening of women with multiple pregnancies could therefore support the timely identification of those at the highest risk.

To date, several studies have investigated the association between pregnancy and the risk of CVD in women.<sup>2-5</sup> Some studies found a J-shaped or U-shaped association between number of pregnancies and risk of CVD, with nulligravity or multigravity associated with an increased risk of coronary heart disease (CHD) and, to a lesser extent, of stroke. Other studies, however, have not been able to replicate these findings, and findings were different in different regions of the world, which raises the discussion on as to whether biological factors related to pregnancy and childbearing or socioeconomic and lifestyle factors associated with parenthood and childrearing explain the apparent associations.

A causal link between pregnancy and CVD risk is biologically plausible and supported by the profound effects of pregnancy on the maternal cardiometabolic system.<sup>6,7</sup> Pregnancy is characterized by physiological changes that are similar to several components of the metabolic syndrome, including a relative degree of insulin resistance, accumulation of abdominal fat, hyperlipidaemia, an increase in coagulation factors, endothelial dysfunction, and increased systemic inflammation. These metabolic changes are of benefit for the mother and infant as they support the growth of the foetus and prepare the mother's body for breastfeeding. While the visible metabolic changes of pregnancy reverse after childbirth, epigenetic modifications induced by high estrogen levels could persist and repeated

pregnancies may have permanent effects on the cardiovascular system that could lead to a higher risk of CVD later in life.

Alternatively, the relationship between the number of pregnancies and maternal risk of CVD in later life may be explained by socioeconomic or lifestyle factors associated with parenthood and childrearing. Women with multiple pregnancies may have larger families and fewer financial resources or may be exposed to greater physical and mental pressures than women with fewer pregnancies (and smaller families). Such exposures might result in poorer housing conditions, stress, reduced physical activity, and increased intake of cheaper and unhealthier foods, which, in turn, could increase their risk of CVD. On contrary, having children might induce a healthier lifestyle in their parents and adult children may also provide important social and material support to their parents as they age.

The relative contribution of the biological factors related to pregnancy and socioeconomic and lifestyle factors related to parenthood and childrearing is uncertain and it may be that much of the association between pregnancy and CVD is mediated by socioeconomic factors and body mass index (BMI). Men do not get pregnant and it is difficult to imagine through what biological mechanism the number of offspring would be associated with the risk of CVD in men. Examination of the relationship between the number of children and the risk of CVD in men is therefore a useful method to address the limitations of studies in women, especially when combined with simultaneous examination in women from the same study.

Few studies have assessed the relationship between the number of children and the risk of CVD, and diabetes, in both women and men. We recently assessed this relationship in the China Kadoorie Biobank, a prospective cohort study of 500 000 men and women recruited from 10 diverse regions in China.<sup>8,9</sup> There have been striking intergenerational changes in family size in China, due partly to the rapid socio-economic developments occurring in China and partly to introduction of the one-child per family policy in the late 1970s which set strict regulations regarding family size. Compared with older generations, individuals born in more recent decades tend to have fewer children, and, particularly in urban areas, increased mean age at first birth. Despite this, there are still large parts of the population with more than 1 child. Our analyses demonstrated that the association between the number of children and the risk of diabetes, stroke, and CHD was largely identical between women and men (Figure). Compared to those with one child, the risk of these

outcomes was higher in those without children and in those with multiple children. Among those with children, each additional child was associated with a small (3-5%) but significant increase in the risk of CHD, stroke, and diabetes. These findings suggest that not only biological factors related to pregnancy and childbearing, but also social, cultural, or psychological factors related to parenthood and childbearing may be important contributors to the link between repeated pregnancy and CVD risk. The increased risk of CVD in women and men without children could be the result of health behaviours or health conditions related to infertility that also might increase the risk of CVD. Alternatively, these individuals may receive limited social or economic support otherwise, in many parts of the world, provided by adult children. Individuals with a limited number of children may be best situated in terms of long-term benefits for CVD, because personal resources may be less likely to be depleted, and adequate support from their children may still be received. Support in achieving and maintaining healthy lifestyle and dietary habits might help in reducing the risk of diabetes and CVD seen in those with larger families.

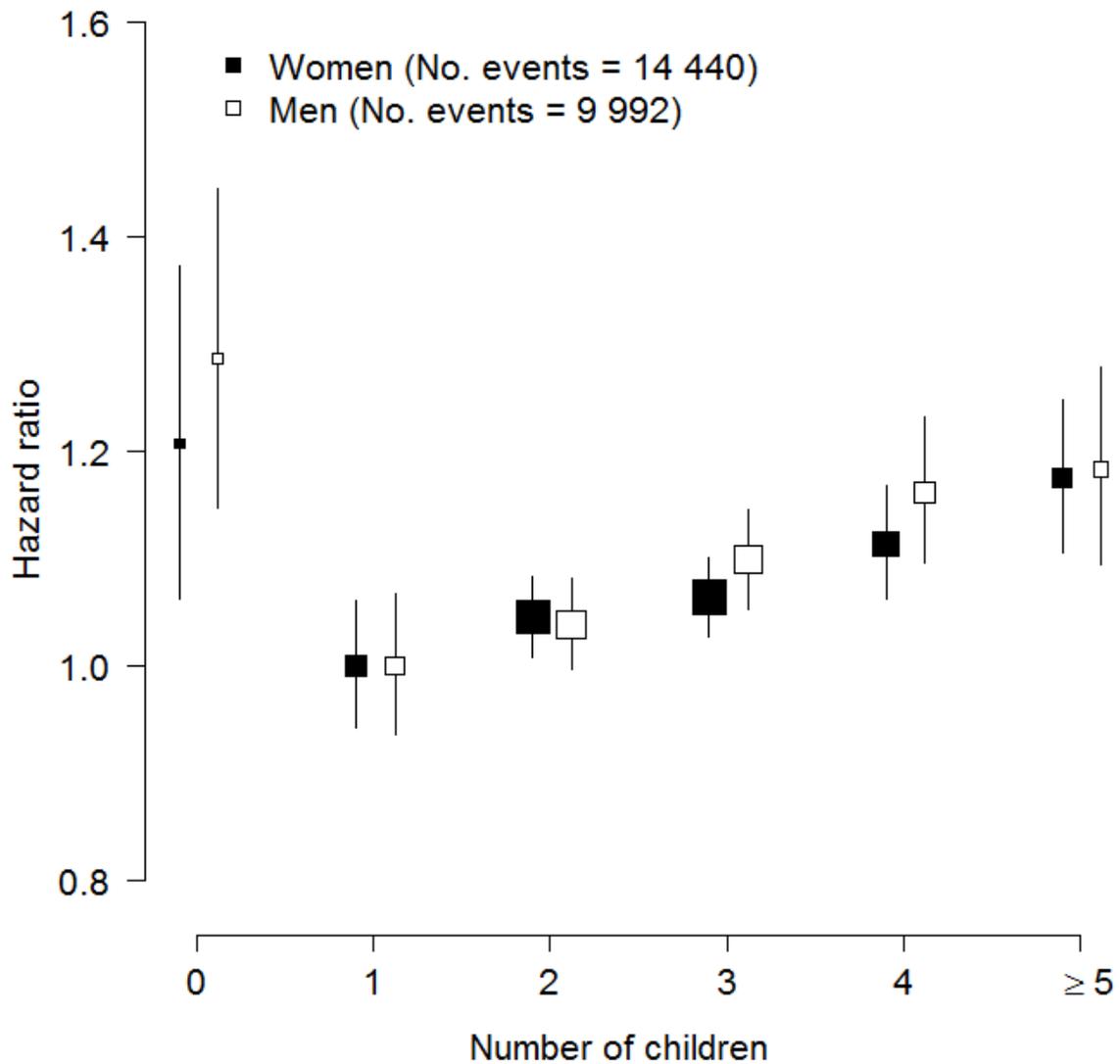
Thus, while pregnancy per se may not be causally linked to CVD, women with a history of pregnancy complications appear to be at increased risk of metabolic and vascular diseases in later life.<sup>1</sup> Gestational diabetes complicates an estimated 5-10% of all pregnancies and is associated with a 7-fold higher risk of diabetes in later life. Women diagnosed with pre-eclampsia, which is estimated to affect 3-5% of pregnancies, are at increased a doubled risk of future cardiovascular events compared to unaffected women. Hence, the onset of pregnancy-associated complications can temporarily unmask the vulnerability of the maternal cardiovascular system and provides a major opportunity for more intensive screening to prevent or delay the re-emergence of CVD in later life. However, awareness of the implications that adverse pregnancy outcomes have for a woman's future cardiometabolic health is limited. At present, care for women with a history of pregnancy complications tends to stop shortly after delivery, may recommence in a subsequent pregnancy, but does not continue during the life-course. Integration of maternal and child health care services with those that identify and manage women at high risk of CVD could help to reduce the burden of CVD for the maximum number of women possible.<sup>10</sup> More systematic collection and analyses of reproductive history, pregnancy complications, and family size, together with data on hormonal status, sexual function and hormone therapies, and long-term follow-up for the onset of CVD is required to strengthen

the evidence needed to inform a life-course approach to the prevention of CVD in both men and women.

## References

1. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European heart journal* 2016;37:2315-81.
2. Dekker JM, Schouten EG. Number of pregnancies and risk of cardiovascular disease. *N Engl J Med* 1993;329:1893-4; author reply 4-5.
3. Kharazmi E, Lukanova A, Teucher B, Gross ML, Kaaks R. Does pregnancy or pregnancy loss increase later maternal risk of diabetes? *Eur J Epidemiol* 2012;27:357-66.
4. Ness RB, Harris T, Cobb J, et al. Number of pregnancies and the subsequent risk of cardiovascular disease. *N Engl J Med* 1993;328:1528-33.
5. Parikh NI, Cnattingius S, Dickman PW, Mittleman MA, Ludvigsson JF, Ingelsson E. Parity and risk of later-life maternal cardiovascular disease. *Am Heart J* 2010;159:215-21.e6.
6. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. *Circulation* 2014;130:1003-8.
7. Lain KY, Catalano PM. Metabolic changes in pregnancy. *Clin Obstet Gynecol* 2007;50:938-48.
8. Peters SA, Yang L, Guo Y, et al. Parenthood and the risk of diabetes in men and women: a 7 year prospective study of 0.5 million individuals. *Diabetologia* 2016;59:1675-82.
9. Peters SA, Yang L, Guo Y, et al. Parenthood and the risk of cardiovascular diseases among 0.5 million men and women: findings from the China Kadoorie Biobank. *International journal of epidemiology* 2016.
10. Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? *Bmj* 2002;325:157-60.

**Figure: Adjusted\* hazard ratios and 95% confidence intervals for incident coronary heart disease associated with number of children**



Data were obtained from reference 9.

\*Analyses are stratified by age at risk and study area, and adjusted for level of attained education, household income, smoking status, alcohol use, systolic blood pressure, history of hypertension, physical activity, body mass index, and history of diabetes. The hazard ratios (HRs) are plotted on a floating absolute scale. Each square (solid for women and blank for men) has an area inversely proportional to the standard error of the log risk. Vertical lines indicate the corresponding 95% confidence intervals (CIs).