

Is being first-born another risk factor for metabolic and cardiovascular diseases?



Ahila Ayyavoo^{1,2}, José GB Derraik¹, Paul L Hofman^{1,2} & Wayne S Cutfield^{*1,2}

¹Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand

²Gravida: National Centre for Growth & Development, Auckland, New Zealand

*Author for correspondence: Tel.: +64 9 923 5118 ■ Fax: +64 9 373 8763 ■ w.cutfield@auckland.ac.nz

Birth rates have been steadily declining throughout the world, particularly in Europe and many Asian countries [1]. This reduction in birth rates is a result of a number of factors, including government policies (e.g. one-child policy in mainland China), greater family planning, personal choice and economic constraints [2]. As a result, there has been a large increase in the number of one-child families and, consequently, a considerable increase in the proportion of first-born children within many populations [2].

Thus, any adverse health outcomes that are associated with being first-born (primogeniture) would likely affect an ever-increasing proportion of the world's population. Notably, only recently has evidence emerged on the consequences of primogeniture on long-term metabolic and cardiovascular health risks.

Early life events, birth weight & later diseases

Traditionally, the causes of adult cardiovascular diseases have clustered into two broad areas: genetic predisposition and lifestyle. However, in recent years, the impact of early life events has been recognized as a third important domain affecting an individual's disease risk in adulthood.

It is now well established that adverse events early in life are associated with long-term changes that may lead to later metabolic and cardiovascular disease [3]. Low birth weight is an indirect indicator of poor intrauterine milieu and adverse health outcomes have been demonstrated in association with decreasing birth weight, even in offspring born appropriate-for-gestational-age. Studies on survivors of

the Dutch famine [4] and research in the UK by Barker [3] have shown that the offspring of mothers exposed to nutritional or physiological stress during pregnancy are at increased risk of metabolic and cardiovascular disease in later life. There is extensive evidence linking a reduction in birth weight with increased risk of insulin resistance, Type 2 diabetes mellitus, hypertension, cardiovascular disease, stroke and cancer [3].

“...first-borns are phenotypically different to later-borns in both childhood and adulthood.”

We have recently observed that, despite similar gestational ages, first-borns were, on average, 250 g lighter than later-borns at birth [2]. This reduction in birth weight among first-borns had been previously noted [5,6], suggesting that primogeniture may be associated with a degree of nutrient restriction *in utero*.

Although the underlying causes are still unclear, there is a suggestion that changes in placentation may account for the observed differences in birth weight [7]. Multiparous women who had earlier uncomplicated pregnancies have better trophoblast invasion and placentation compared with women who are pregnant for the first time [8,9]. Beneficial immunomodulating effects are also seen in multiparous pregnancies [8]. These factors could account for improved nutrient flow to later-born fetuses, consequently improving fetal growth in later pregnancies.

Exposure to nutritional or physiological insult at different periods of gestation has been associated with various adverse outcomes in offspring [4]. However, the timing of possible stressors to

Keywords

- birth order ■ cardiovascular disease ■ diabetes ■ first-born
- insulin sensitivity
- phenotype

first-born fetuses is not known. A stress early in pregnancy does not affect birth weight as much as insults late in the third trimester. Thus, first-borns may be subjected to an adverse *in utero* environment late in pregnancy, which would explain a reduction in birth weight. Alternatively, it is possible that first-borns may be subjected to a less favorable intrauterine environment throughout the entire pregnancy.

Phenotypic differences & cardiovascular risk

Irrespective of the timing and nature of possible stressors *in utero*, it is clear that first-borns are phenotypically different to later-borns in both childhood and adulthood [2,5,10]. Studies have shown that first-born children were taller (with a progressive reduction in height with subsequent births) and had greater circulating IGF-I concentrations than later-born children [2,10]. There was a reduction of 1.3 cm in height in second-born children compared with first-borns, with a further 2 cm decrease from second- to third-born children [10]. Other studies revealed similar difference in height between first- and later-borns [11]. Taller stature in childhood is positively associated with overweight status and obesity later in life [12], and a large study in Brazil of over 2000 men found that first-borns were taller and had greater fat mass than later-borns [13].

There is also mounting evidence that first-borns have an increased risk of adverse health outcomes later in life. Earlier studies have shown that first-borns were more likely to develop Type 1 diabetes mellitus [14], allergic disorders [15] and psychological issues [16]. In a prospective cohort study, primogeniture was a significant risk factor for increased adiposity in young adulthood [17]. Nearly four decades ago, a study in young adults suggested that first-borns were at a greater risk of developing hypertension [18]. An unpublished study presented at an American Heart Association forum 12 years ago by Ferratini and colleagues indicated that primogeniture was associated with an increased rate of heart disease in a population of 358 patients [10]. The previously mentioned Brazilian study also found that, in association with their increased fat mass, first-borns had higher metabolic risk z-scores compared with later-borns [13]. The metabolic risk z-score was calculated as the average of the z-scores of fat mass, lipid profile and blood pressure, with a higher score indicative of a higher risk of the metabolic syndrome [13]. The same research group observed a similar increase in metabolic risk among first-born women [19].

Importantly, we have recently shown that insulin sensitivity (as determined by Bergman's minimal model) was 21% lower in first-born children compared with later-borns [2]. It is worth noting that neither a reduction in birth weight nor current adiposity explain the observed difference in insulin sensitivity, as both were accounted for in all statistical models [2]. To put the observed reduction in insulin sensitivity in context, the magnitude of the change (20%) is similar to the increase seen with medications used to treat diabetes in adults, such as metformin [20].

A reduction in insulin sensitivity (insulin resistance) with compensatory hyperinsulinism is associated with metabolic and cardiovascular diseases. Insulin resistance leads to reduced endothelial cell production of nitric oxide, greater myosin light chain activation with vasoconstriction and reduced skeletal muscle glucose transport [21]. In a cohort of 208 apparently healthy middle-aged nonobese men, insulin resistance was an independent predictor of many disorders 4–11-years later, including Type 2 diabetes mellitus, hypertension, coronary heart disease, stroke and cancer [22]. Facchini *et al.* showed that 36% of individuals in the least insulin-sensitive tertile suffered one or more of these adverse events; by contrast, no events were recorded among individuals in the most insulin-sensitive tertile [22].

“...reduction in insulin sensitivity ... and ... increased blood pressure seen in first-borns may have long-term consequences for cardiovascular health.”

Furthermore, 24-h ambulatory blood pressure monitoring showed that first-born children also had higher daytime systolic (+5 mmHg) and diastolic (+4 mmHg) blood pressure [2]. This is equivalent to the observed difference in systolic and diastolic pressure between an obese child and a child of normal BMI [23]. Higher blood pressure tracks from childhood into adulthood and the prevalence of hypertension is 3.6-times more common in those with a childhood blood pressure in the highest quintile [24]. In the prospective 1993 Pelotas birth cohort [5], the difference in systolic blood pressure in first-borns was attributed to early catch-up growth and the difference in diastolic blood pressure to reduced physical activity. Nonetheless, the increased blood pressure seen in first-borns may

have long-term consequences for cardiovascular health.

Future perspective

There is mounting evidence suggesting that primogeniture is a contributing factor to overall metabolic and cardiovascular disease risks in later life. However, birth order alone does not predict metabolic or cardiovascular disease. The relevance of these findings will likely continue to increase with the worldwide trend towards small nuclear families. Notably, first-borns are the largest identifiable study group (accounting for more than half of the world's population), so that any associated health risks could have enormous public health consequences.

Further research is warranted to address a number of important questions associated with birth order. What is the contribution of primogeniture across ethnicities to the development of diabetes, hypertension, heart disease and other insulin-resistant disorders? Do the adverse changes seen in first-born children persist into adult life? It seems that altered placental nutrient supply to first-born fetuses may

influence metabolic programming via mechanisms other than those that lead to a reduction in birth weight. So, what are the triggers and mechanisms underpinning these programmed changes in first-borns? Such data would be valuable to better evaluate the extent of the disease risk among the ever-increasing proportion of primogeniture worldwide.

Financial & competing interests disclosure

The authors' research findings referred to in this article were supported by funding from Gravidia: National Centre for Growth and Development (New Zealand) and the Australasian Pediatric Endocrine Group. They also acknowledge the Paykel Trust for long-term funding of the Maurice and Agnes Paykel Clinical Research Unit at the Liggins Institute, University of Auckland. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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