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Letters

Comment

—to: Hales CN, Ozanne SE (2003) For Debate: Fetal and early postnatal growth restriction lead to diabetes, the metabolic syndrome and renal failure. Diabetologia 46:1013–1019

To the Editor: In their recent For Debate article, Hales and Ozanne gave an impressive overview of the overwhelming body of data accumulated over the past decade that seems to indicate a causal relationship between low birthweight and later development of the metabolic syndrome X [1]. More specifically, they state that fetal and early postnatal growth restriction lead to diabetes, the metabolic syndrome X and renal failure. However, the authors do not take into account a fundamental concept that is critically related to the pathophysiology of the metabolic syndrome X and its possible relation to low birthweight: obesity is known to be the key feature of human metabolic syndrome X. This factor requires explicit consideration. From a public health perspective, overweight is recognised as the major cause of the dramatic increase in the prevalence of Type 2 diabetes, the metabolic syndrome X, and critical cardiovascular endpoints observed in recent years [2]. To our knowledge, however, no study currently exists that describes an *independent* association between low birthweight and obesity in later life. Only inconsistent data are available on the risk of obesity in later life in low birthweight subjects, as recently reviewed by Oken and Gillman [3]. From these epidemiological data, it cannot be concluded that low birthweight is an independent risk factor for obesity in later life.

In contrast, epidemiological and experimental data exist that suggest that high birthweight as well as rapid neonatal weight gain are *independent* risk factors for overweight and obesity in later life [3, 4, 5]. It is worth noting that evidence from the literature has confirmed that rapid neonatal weight gain is the "missing" pathophysiological link between low birthweight and later increased risk of adipogenic and metabolic conditions, as we proposed ten years ago [4]. Clearly, there is a supposition that high and rapid neonatal weight gain is caused by neonatal overnutrition. Indeed, overfeeding in the neonatal period has been shown to lead to rapid neonatal weight gain, followed by overweight and associated metabolic disturbances later in life [3, 4, 5, 6, 7]. Moreover, in animal models of early postnatal overfeeding resulting in rapid early weight gain, all key features of the metabolic syndrome X were observed during life, including early obesity, impaired glucose tolerance and increased blood pressure [7].

Unfortunately, these observations are almost completely ignored in the article by Hales and Ozanne. Moreover, they propose the opposite in the title of their article: "...*early postnatal* growth restriction leads to diabetes, the metabolic syndrome and renal failure". This is an obvious contrast to even their own findings, which are mentioned briefly in the For Debate article and have recently been published in more detail [8]. Here, Hales and Ozanne report not only increased metabolic risk but also dramatically decreased life span in mice that had experienced growth restriction during intrauterine life, but only when followed by diet-induced rapid neonatal weight gain.

Impaired fetal growth is very likely to be an indicator of a maternal disease and/or deleterious intrauterine exposures. Moreover, it may also be indicative of subsequent alterations in neonatal environmental conditions, e.g. in terms of neonatal overfeeding. Such unfavourable neonatal conditions, rather than restricted intrauterine growth per se, may be a cause of the lasting outcome, and should be addressed in more detail in future studies. Recognising the potential of this approach appears to us to be a real step forward in the fields of fetal and neonatal programming and perinatal preventive medicine.

In conclusion, we highly value the contributions and efforts made by Hales and Ozanne to take forward research on fetal programming. Recognising that problems arise on both ends of the birthweight spectrum, however, will be as crucial in terms of research and clinical implications as investigating which maternal diseases or early postnatal events are of pathophysiological importance for perinatal programming [4].

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