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EDITORIAL

Metabolic outcomes in very low birthweight and preterm infants in later life☆,☆☆

Desfechos metabólicos posteriores em recém-nascidos de muito baixo peso ao nascer e pré-termos

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Survival for very low birthweight (VLBW) infants has improved dramatically over the last 2 decades. This has shifted the aim of neonatal care from one that focuses purely on short term survival to one that considers the life-long impacts of preterm birth.[1] Neonatologists must, of course, continue to strengthen their efforts to reduce key neonatal morbidities such as necrotizing enterocolitis, sepsis and chronic lung disease, but must now consider the impact of nutrition and other interventions over the life course. There are strong data to show that improved neurocognitive outcomes are associated with higher early nutrient intakes. However, the emerging discipline of 'Developmental Origins of Health and Disease' (DOHaD) has increased awareness of the associations between higher nutrient intakes and more rapid growth in early life and worse long-term metabolic outcomes such as cardio-vascular disease and type 2 diabetes.[2,3] This risk seems especially high in those who are born in utero growth-restricted (IUGR), but the independent impact of prematurity has not been well studied.[4] The paper by Heidemann et al.[5] is important because it highlights the issue that adverse metabolic effects may be apparent in early infancy in those born preterm, and asks clinicians to consider what practical steps can be taken to reduce their later life consequences.

Heidemann's cross sectional study included VLBW preterm infants recruited from a single tertiary center in Brazil who were followed up in a well organized outpatient clinic, and explored the relationship of early neonatal exposures on later metabolic syndrome-like symptoms (MSL). Defining the 'metabolic syndrome' in childhood is challenging and few comparable studies exist; furthermore there are no agreed standards or definitions that allow a comprehensive diagnosis, and virtually no longitudinal data exist. Using a valid and practical definition of the metabolic syndrome is therefore challenging, but many studies have explored insulin resistance in the context of DOHaD.[6] Heidemann et al. used a similar definition to that developed to describe an abnormal metabolic phenotype in adolescents,[7] but whether such a definition will ultimately be shown to be a valid and robust marker of later outcomes when applied in infancy remains to be determined.

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Follow-up studies of children born preterm are notoriously difficult, and even the well-recognised international cohorts suffer from important attritional losses over time.[8] In Heidemann's study, children who attended at least 3 follow-up visits were eligible for inclusion. Nevertheless, it is important to consider the possibility that those who attended for frequent follow-up may not be representative of those who were in-frequent attenders, or worse still, those who did not attend at all. Data from other settings suggest those at highest risk of morbidities may sometimes be the most difficult to follow up.[9] Families from less affluent backgrounds may struggle with costs of transport to attend clinics, or the costs of taking time off work, and may live in environments with less access to exercise and opportunities for physical activity. These children may also have different background rates of breastfeeding, or be fed using sub-optimal diets during early infancy. Adjusting for such factors in observational studies is extremely complex, and even then, determining whether they are on the causal pathway to MSL is challenging using observational cohort designs.

The study recorded a range of neonatal variables, including nutritional exposures such as the use of amino acids in parenteral nutrition (PN) in the first 24 h of life. The benefits and risks of early PN remain uncertain although most NICUs now consider it routine.[10] There was no evidence that early PN exposure increased the later risk of MSL, but the data collection and analysis was not able to account for actual macronutrient intakes either from PN or subsequent enteral intakes whilst on the Neonatal Intensive Care Unit (NICU). Data from term infants show that increased dietary protein intakes most often through the consumption of infant formula milk (that has higher protein concentrations than breastmilk) are associated with an increased risk of later obesity.[11] Preliminary data suggest the effect is likely to be mediated through IGF-1 and other endocrine pathways. Whether similar long-term adverse MSL effects exist in VLBW infants is uncertain. However, this needs to be considered alongside the data that show that IGF-1 levels in VLBW are frequently much lower than fetal references, and that these low levels may themselves impair optimal brain growth.[12] It is possible, therefore, that a feeding strategy on the NICU that optimizes IGF-1 levels, and thus brain development, may also increase risks of later obesity.

Heidemann et al.[5] also explored breast feeding status at 6 months of age and the occurrence of MSL but were unable to demonstrate any association. Data from other settings demonstrate that breastfeeding status is a key modulator of later metabolic health and show that infants who were breast-fed have lower blood pressure and improved bone health in later life.[13,14] Breast-milk exhibits a dose-response effect in these studies, with evidence that even a few months of breast-feeding may be beneficial for neurocognitive outcomes and metabolic health. Breastmilk may therefore be important even when it is not exclusive, and where it doesn't continue until 6 months of age, as recommended by the WHO and other organizations. Few mothers of preterm infants are able to maintain breastfeeding for prolonged lengths of time: in Heidemann's study <15% of infants were exclusively breastfed at 6 months corrected age.

Determining the impact of prematurity *per se*, rather than the events leading to preterm delivery is virtually impossible. Preterm birth is frequently the end result of a compromised pregnancy. The mothers of infants in this study may have had pre-pregnancy complications such as hypertension, obesity or diabetes. Alternatively, they may have developed metabolic or other complications during pregnancy, including gestational diabetes and placental dysfunction that either predisposed to early labor or was severe enough to justify elective delivery by cesarean section. Other preterm infants may have been relatively healthy as a fetus, and been born vaginally, but may have been born prematurely due to some other complication such as cervical incompetence or other factors leading to spontaneous preterm delivery. Determining whether the MSL observed is a reflection of in utero exposures, or simply a consequence of early ex utero life is impossible. In the study, over 40% of the infants were small for gestational age (SGA). Whether SGA in this study is an indication that the infants were IUGR is difficult to determine. Importantly, it must be remembered that it is possible for an infant to be IUGR but still be born >10th percentile.[15] Whether the effects observed in this study are primarily due to prematurity or to IUGR is difficult to determine.

The prevalence of MSL in this study was alarmingly high, with >75% of infants having at least one abnormal measure, although the authors acknowledge that the true prevalence of abnormal metabolism may be lower. Regardless, this appears substantially higher than at least one other contemporary Brazilian study.[16] Around 25–30% of infants in Heidemann's study appear to have some evidence of abnormal lipid profiles but there are few comparable data, and it is difficult to know whether such abnormalities will track into later life. There are overwhelming data to show that rates of childhood obesity are rising around the world, reaching epidemic levels in some countries. In this study almost 20% of infants were classified as overweight or obese. Similar to lipid profiles, it is difficult to know how obesity in infancy may reflect measures of obesity in later life but there are considerable observational data to show that children who are obese are much more likely to be obese as adults. This may reflect 'tracking' of obesity throughout life, or simply reflect the fact that the socio-demographic factors linked to obesity in childhood are also likely to be present in later life.

Perhaps most concerning is the high prevalence of hypertension: 57.5% of infants had high blood pressure, and those who had been diagnosed with periventricular leukomalacia were at increased risk (OR 2.34). These findings are in keeping with existing literature showing increased risks of hypertension in preterm born young adults.[17,18] Blood pressure also appears to 'track' quite strongly into later life compared with other measures of MSL[19] and raises the possibility that small differences in early infancy might result in big differences in later life. In the large Swedish EXPRESS cohort of extremely preterm infants, blood pressure at 6 years of age was found to be in the normal range, although it was slightly higher than term-born peers.[20] The EXPRESS study showed there were no strong associations with perinatal variables, but blood pressure was associated with gestation and BMI. Interestingly they had shown similar effects at 2.5 years similar to the age studied by Heidemann

et al.[5] In the EXPRESS study, detailed echocardiography demonstrated a unique cardiac phenotype characterized by a smaller left ventricle with altered systolic and diastolic functions than same-aged children born at term.[21] Hypertension may not simply be a marker of the 'metabolic syndrome' *per se*, but it reflects differences in early life environments that permanently change cardiac structure due to the fact that preterm infant cardiac output does not need to be directed back toward the placenta.

The mechanisms by which the early life of VLBW infants might program later metabolic outcomes are numerous. Animal studies have demonstrated a range of possible mechanisms such as decreases in organ size (e.g. decreased early nephron number or growth), altered endocrine setpoints, DNA methylation or other epigenetic changes, and permanent alterations to the gut microbiome.[22–24] Without knowing the relative contribution each of these mechanisms may play it is difficult to know how we might best reduce or prevent these later-life complications. It is also possible that there is reverse causation: perhaps infants who develop later hypertension or obesity were those best able to survive the challenges of very premature delivery?

So what practical messages can clinicians gain from this study? It is tempting to suggest that we should always measure blood pressure or perform echocardiography in follow-up clinics, but what would we do with the findings, and would this simply generate parental anxiety? There is no current evidence that early drug intervention is beneficial, but perhaps children born preterm should be offered a ''routine medical review'' when they become adults? But who would provide this service and would teenagers and young adults attend? There seems to be no harm in providing healthy lifestyle advice about diet, growth and physical exercise; indeed other follow-up studies in preterm children have shown that growth patterns after infancy were much stronger predictors of abnormal metabolism in early adolescence than NICU or infant growth and nutrition.[4] However, it is difficult to provide clear advice on interventions in NICU period without more data: restricting catch-up growth or nutrient intake at a critical stage of development may do more harm than good. Until then, clinicians must walk the tightrope of optimizing survival and brain outcomes with good nutrition (and especially mothers' own breast milk) in early life, whilst at the same time hoping they do not adversely affect later metabolic outcomes.

Conflicts of interest

Dr. Embleton declares that he has received funding from the UK NIHR, and commercial manufacturers of infant milk formula for research studies in preterm infants, but has no specific financial or other conflicts. Dr. Wood has no conflicts to declare.

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