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EDITORIAL

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Does low birthweight matter?

In Sweden, about 7000 infants are born preterm every year, before 37 weeks, and they account for 4%-5% of residents under the age of 18. There is an ongoing debate about how preterm birth affects health outcomes during the early postnatal weeks and in adult life. For example, preterm birth has been associated with a higher incidence of cardiovascular, metabolic and mental health issues in adulthood.[1]

In this issue of *Acta Paediatrica*, Forsum et al[2] used weight and air-displacement plethysmography to investigate the fat mass and fat-free mass of 188 preterm children born at 23.2-36.9 weeks of gestation, including 73 born very and extremely preterm before week 32. These are called the early preterm group in the paper, and any aged 32 weeks or more are called late preterm. The authors compared them with 253 age-matched full-term controls when they reached four years of age. The findings confirmed other pre-pubertal studies that infants born before 32 weeks tended to weigh less and be shorter than full-term controls.[3-5] The early preterm girls in the Forsum et al study had a significantly lower body mass index (BMI) than the girls in the full-term control group, but not the early preterm boys. Both the early preterm girls and boys had less fat mass than the corresponding controls. The early preterm girls also had less fat-free mass than their full-term peers. The late preterm girls and boys did not differ from the full-term controls with regard to fat mass. Gestational age was a weak, but significant, positive predictor of the investigated growth variables at follow-up in girls, but not in boys.[2]

One of the strengths of the Forsum et al study, apart from the relatively large cohort, was that it was conducted systematically and methodically, with little variations in age between the preterm and full-term groups at follow-up.

In air-displacement plethysmography, body composition is estimated from density, which is then divided into fat mass and fat-free mass. Total body mass thus equals fat mass plus fat-free mass. Fat-free mass comprises skeletal muscle, organs, bone and supporting tissues. Height is the most important factor in fat-free mass. Air-displacement plethysmography is considered the method of choice for measuring body composition in children, and it is more readily accessible than dual-energy X-ray absorptiometry (DEXA), which is mostly used for measuring bone mineral density. However, DEXA measures bone mineral content directly, which means that it eliminates one of the major sources of fat-free mass variability in the two-compartment model.

Several studies of pre-pubertal children have found similar results to Forsum et al, as the authors pointed out. Huke et al used impedance analysis to evaluate fat mass in 116 preterm born children when they reached 5-7 years of age and found that they were shorter, weighed less, had lower BMIs and had less fat mass than full-term controls.[3] Another study investigated 200 preterm children, including those born very preterm and late preterm, using DEXA. After adjusting for height, the preterm group had less fat mass, but similar fat-free mass, than the full-term group. Being female strongly predicted elevated fat mass.[4] Gianni et al[5] found that preterm born children had lower fat masses, heights and weights at five years of age than full-term controls.

Our smaller study of four-year-olds differed to Forsum et al as the preterm and full-term groups had similar BMIs, weights and adjusted height standard deviation scores at follow-up.[6] After adjusting for height, the preterm group had a greater fat mass and lower fat-free mass than the full-term subjects.

All these findings lead us to conclude that preterm subjects have a favourable fat mass body composition during pre-pubertal years, when they remain thin and short.

In 1992, Hales and Barker proposed the thrifty-phenotype hypothesis[7] for the aetiology of type 2 diabetes and suggested that low-birthweight infants had impaired beta-cell growth. As long as the individual remained undernourished, the need for insulin was small. However, if the infant ate too much and experienced rapid catch-up growth, the reduced beta-cell function could trigger diabetes. The debate continues whether a low birthweight, per se, or weight gain in infancy can predict a worse metabolic outcome in adulthood.

In accordance with this, a study of preterm subjects who experienced rapid catch-up growth throughout infancy showed a later risk of increased intra-abdominal adiposity, and altered, decreased insulin sensitivity.[8] In that study, preterm infants who were born small for gestational age seemed to have the greatest risk.

Forsum et al[2] found that the early preterm girls had a mean birthweight z-score of −0.93 ± 1.4. That group probably included infants born appropriate for gestational age and small for gestational age, below the 5th percentile or below—2 standard deviations (SD). At a mean age of 4.4 years, the early preterm girls were relatively lighter and shorter than average, with a mean weight of—1 SD compared to the reference value for Swedish children of the same age. At follow-up, some early preterm girls weighed<−2 SD of the reference weight.

Z-scores for growth variables at follow-up were not presented. Thus, it was difficult to estimate adjusted catch-up growth variables. Overall, all the preterm girls appeared to have had a more distinct height catch-up, from birth to four years, compared to the preterm boys. However, the question remains about whether the different preterm groups differed in height SD score (SDS) relative to their predicted target height SDS at follow-up? One way to estimate this would be to calculate the difference in height SDS in relation to target height SDS. Further studies might focus on preterm infants born small for gestational age and the possible effects of catch-up or lack of catch-up growth on the studied parameters.

Early nutrition may also be of importance for later body composition. Formula feeding or breastfeeding during infancy might affect body composition differently, as indicated by magnetic resonance scans at term-equivalent age in very preterm infants.[9]

Forsum et al did not provide information about early nutritional intake in the different groups. It would also have been interesting to have data on certain metabolic features, like the glucose or fasting insulin levels of these children. A study by de Jong found that two-year-old subjects born preterm had lower body mass indexes (BMI) and lower fat mass, but higher glucose levels, than full-term subjects.[10]

What will the effects of puberty be on these preterm groups? At the age of 20, DEXA showed that a large group of individuals born preterm had greater total fat mass and greater lean body masses, adjusted for height SDS, than full-term individuals.[11] Therefore, it will be important to follow the Forsum et al cohort to evaluate the impact of puberty.

The association between fat distribution per se and low birthweight is of interest. The waist-to-hip ratio or the waist circumference can shed some light on fat distribution. Excess visceral fat has been associated with insulin resistance. In preterm children, central adiposity and possible correlations with prematurity have shown different results.[3,5]

The finding by Forsum et al that gestational age was only correlated to body composition markers in girls, but not boys, could be due to gender differences, a hidden impact of being born small for gestational age, and/or, a difference in catch-up growth between very low-birthweight girls and boys. Moreover, this gender difference might change over time. An alternative, but rather unlikely, theory is that gender variations might be explained by different brown adipose tissue content. However, in adult subjects born preterm, both sexes exhibited brown adipose tissue.[12]

Leptin is a circulating hormone derived from adipocytes that are released in proportion to the adipose tissue mass. Lack of adipose tissue results in a leptin deficiency, severe hyperglycaemia and intractable diabetes. Thus, to a certain extent, the effects of fat mass could be beneficial. In the Forsum et al[2] study, both full-term and preterm girls tended to have larger amounts of fat relative to their weights than boys. We found similar results at 9 years of age, where leptin levels were slightly higher in girls than in boys. Leptin levels were strongly correlated with the BMI SDS, but this was not observed in adult women born preterm.[13]

It is possible that pre-pubertal females who are born small for gestational age and exhibit high leptin levels, relative to their BMI SDS, may be protected from later hyperglycaemia.[13] Subjects may have different abilities to compensate for adverse metabolic outcomes, independent of body composition. The leptin-to-adipose tissue ratio might be particularly important in preterm subjects with a risk of hyperglycaemia in adulthood. Thus, the development of type 2 diabetes might be related to a low leptin-to-adipose tissue ratio.[14]

Frequent follow-up of growth variables in preterm children is important. In relation to life expectancy, cardiovascular outcomes probably have a greater impact than body composition, although the latter probably does play a minor role. A bigger threat may come from a combination of growth failure and behavioural and eating disorders.[15]

Forsum et al are to be congratulated for describing a large study population that, hopefully, will be further monitored and can provide a future bank of knowledge.

CONFLICTS OF INTEREST

None.

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