Birthweight z-score and fat-free mass at birth predict body composition at 3 years in Danish children born from obese mothers

Berglund, Nanna Reinholdt; Lewis, Jack Ivor; Michaelsen, Kim F.; Mølgaard, Christian; Renault, Kristina Martha; Carlsen, Eva M

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BACKGROUND

With increasing global prevalence of overweight and obesity in both child- and adulthood, further research is needed to understand the origins and the critical time periods that could possibly increase the risk of obesity and later adverse health outcomes. Several studies have shown that maternal obesity is associated with high offspring birthweights, which can further increase the risk of becoming overweight or obese later in life. However, these studies have mostly relied on surrogate measures of adiposity and those with more specific measures of body composition are limited. Of those that investigate body composition, it seems like...
positive association that exists between maternal pre-pregnancy body mass index (BMI) and infant body fat, while the association with infant lean mass is less clear.\textsuperscript{2,3} Additionally, the majority of the studies fail to investigate whether the increased body fat tracks into later life. Of the few studies which have investigated a tracking of body composition, none have focused on children from obese mothers.\textsuperscript{4–6} One of the studies was conducted by Forsum et al., who investigated body composition in 253 healthy Swedish children at 1 week, 12 weeks and at 4 years of age by the use of air displacement plethysmography (ADP).\textsuperscript{5} They showed positive associations between fat-free mass (FFM) and fat-free mass index (FFMI) at 1 and 12 weeks, and FFM and FFMI at 4 years of age. Additionally, they found positive associations between fat mass (FM), fat mass index (FMI) and body fat in % at 12 weeks and the same variables at 4 years of age, thus supporting tracking of body composition from birth through early childhood and the importance of optimal intrauterine growth.\textsuperscript{6} We have identified that an increased fat mass present in newborns of obese mothers has the potential to track into later life and confer negative effects on their future body composition and thus metabolic health. This study aims to investigate such programming using body composition data from birth and at 3 years in Danish children born from obese mothers.

2  |  METHOD

2.1  |  Study design

Analyses are based on data from the observational cohort study SKOT II (SKOT; Danish abbreviation of small children’s diet and well-being), which is described in detail elsewhere.\textsuperscript{7} In brief, the study was performed at the department of Nutrition, Exercise and Sports, University of Copenhagen between 2011 and 2015, with participants recruited from the Treatment of Obese Pregnant Women (TOP) intervention study.\textsuperscript{9} The main objective of SKOT II was to examine how maternal obesity (pre-pregnancy BMI $\geq 30$ kg/m\textsuperscript{2}) affected offspring growth and development at 9–36 months.\textsuperscript{7} During the study period, infants were examined at 9 months $\pm$ 2 weeks, 18 months $\pm$ 1 months and 36 months $\pm$ 3 months.\textsuperscript{7} Additionally, all infants had their body composition measured at birth by dual-energy X-ray absorptiometry (DXA) scans in connection with a previously conducted study.\textsuperscript{9} Data on body composition and anthropometry were derived from 183 infants included in the SKOT II final analysis (Figure S1).\textsuperscript{7}

2.2  |  Maternal and offspring data

Infant birthweight, length and gestational age were obtained from birth records, and the remaining measurements, except from newborn body composition, were carried out at the examinations during the SKOT II cohort follow-up visits.\textsuperscript{7}

2.3  |  Body composition assessment at birth and at 3 years of age

Newborn body composition was assessed by DXA scans (DXA Hologic 4500) within 48 h after birth.\textsuperscript{9} The abdominal region was identified by use of the inbuilt paediatric software with the purpose of estimating abdominal FM and FFM.\textsuperscript{9} More details on newborn body composition assessment in these newborns are described in Carlsen et al. (2014).\textsuperscript{9}

At 3 years, child body composition was estimated by bioelectrical impedance analysis (BIA). The measurements were carried out using a single frequency (50 kHz) tetra polar bioelectrical impedance analyzer (Quantum III, RJL Systems) with measurements performed in duplicate and the child in a supine position wearing light clothing.\textsuperscript{10} A signal electrode was placed on the right foot over the distal portion of the second metatarsal, and the detecting electrode was placed at the anterior ankle. Another signal electrode was placed on the right hand above the metacarpophalangeal joint of the middle finger. The corresponding detection electrode was placed on the right hand as well, but on an imaginary line bisecting the ulnar head. The mean values from two measurements of resistance, reactance and impedance were registered. A predictive equation was used to estimate FFM from the resistance

Key Notes

• Studies investigating associations between body composition at birth and later in life are limited.
• We found that infants born with a higher birthweight z-score (BWZ) were taller and heavier in terms of fat mass (FM) and fat-free mass (FFM) at 3 years, and that FFM at birth tracks into early childhood.
• Our findings support tracking of body composition in early life and the importance of intrauterine growth.

Maternal BMI was calculated as weight (kg)/height (m)$^2$, and maternal gestational weight gain (GWG) was divided into three categories: insufficient (<5 kg), recommended (5–9 kg) and excessive (>9 kg) according to the recommendations for obese pregnant women made by Institute of Medicine (IOM).\textsuperscript{10} Exclusively breastfeeding was defined as receiving only breastmilk, vitamins and water and was reported by the mother.\textsuperscript{7} Birthweight z-scores (BWZ) were calculated by adjusting birthweight for gestational age and sex using the INTERGROWTH 21st software.\textsuperscript{11} Birthweight z-scores were categorised into small for gestational age (SGA), appropriate for gestational age (AGA) and large for gestational age (LGA), and were defined by a birthweight z-score below $-2$ SD, between $-2$ SD and $+2$ SD and above $+2$ SD, respectively.\textsuperscript{11} Weight, height and BMI at 3 years were converted to age and gender-specific z-scores using WHO growth standards and the WHO Anthro software.\textsuperscript{7,12}
index. This equation was generated by Ejlerskov and colleagues in a very similar population (Danish children of 3 years) using DXA as a reference method. As described by Ejlerskov et al. (2015), the error associated with discrepancies in DXA and scale weights is disproportionally inflated in the predicted fat mass, being the smaller compartment. In addressing this error, we have followed their recommendation to use an adjusted weight to predict FM. This adjustment was generated by regressing DXA weight on scale weight for the population originally used for equation generation and took the form \(0.981 \times \text{weight}_{\text{scale}} + 0.374 = \text{weight}_{\text{adj}}\). This approach results in a FM estimate more closely representing the true FM according to DXA. The equations were as follows:

\[
\text{FFM (g)} = 3272 + \text{RI} \times 2238 + \text{wt} \times 76.8 + \text{ht} \times 417.6 + \text{sex} - 2784.4
\]

\[
\text{FM (g)} = \text{weight}_{\text{adj}} \times 1000 - \text{FFM}
\]

Body fat in % = \(\frac{\text{FM}}{\text{FM} + \text{FFM}} \times 100\)

RI was the resistance index (height (cm)^2/resistance (Ω)). \(\text{wt}\) was the digital weight (kg), \(\text{ht}\) the measured height (cm), and sex was categorised as male = 1 and female = 0. In addition, FMI was calculated as total FM (kg)/height (m)^2 and FFMI was calculated as total FFM (kg)/height (m)^2 to take natural variation in FM and FFM due to body size into account. Newborn FMI and FFMI were not estimated due to uncertainty in newborn length measurements made at the hospitals.

2.4 | Ethics

The cohort study included in this present paper was approved by the Ethics Committee for the Capital Region of Denmark (H-3–2010–122), and written informed consent statements were obtained from all parents.

2.5 | Statistical analyses

The study sample only included infants with complete measurements of the exposure and outcome variables, and significance was defined as \(p \leq 0.05\) in all analyses. Normality of continuous variables were verified by Shapiro–Wilk tests for normality and by visual inspection of histograms and QQ-plots. Continuous variables were described as mean ± SD or median (interquartile range (IQR)) depending on their normality, and categorical variables were expressed as frequency (%). Differences between means, medians and proportions were detected by Student’s t-tests, Mann–Whitney U-tests and chi-squared tests, respectively. Separate multiple linear regression analyses were conducted to investigate the association between body composition at birth as the main exposure (BWZ, FFM, FM, body fat in %, total abdominal FFM and total abdominal FM) and anthropometry and body composition at 3 years of age as the main outcome (FFM, height, FFMI, FM, body fat in % and FMI). Potential confounding variables were identified by univariate linear regression models and a priori knowledge (Table S2). Confounders were considered for inclusion in linear regression models if they changed the effect of the main exposure or if they were correlated with the outcome. Models were adjusted for sex, age at the 3 years examination, gestational age at birth, maternal BMI at 9 months, GWG, maternal education, maternal age, parity, total duration of breastfeeding and age of introduction to complementary food. When examining associations between BWZ and the outcomes at 3 years, models were not adjusted for sex and gestational age. Results of the linear regression models are presented as beta coefficients, 95% confidence intervals and \(p\)-values. All statistical analyses were performed in R-studio version 1.1423 (The R foundation for statistical Computing).

3 | RESULTS

3.1 | Data collection

Of 183 infants included in the final SKOT II analysis, we excluded 80 with incomplete body composition data at birth or 3 years. Our final analysis included 103 infants (Table S1). Included and excluded participants were comparable (Table 1).

3.2 | Maternal and offspring characteristics

All mothers were obese at birth, most had experienced excessive GWG, and the majority were expecting their first child (Table 1). Only one of the mothers smoked (data not shown) and over 50% had a medium or long term education.

Median (25th, 75th percentile) infant birthweight was 3720 g (3395–4040 g) and mean length was 52.7 ± 2.2 cm. Most of the infants were born AGA (\(n = 72, 80\%\)), while 16 (18%) were born LGA. Values for offspring body composition are shown in Table 2. On average, infants were exclusively breastfed for 3.0 months and partially breastfed for 6.5 months. The majority of infants were introduced to complementary foods (CF) between 4 and 6 months (\(n = 87, 86\%\)) and just two were still breastfed at 18 months.

3.3 | Predictors of body composition at 3 years of age

Separate linear regression model outputs are presented for the associations between newborn body composition (BWZ, FFM, FM, body fat in %, abdominal FFM and abdominal FM) and anthropometry and body composition at 3 years of age (FFM, height, FFMI, FM, body fat in % and FMI) in Tables 3 and 4.

Birthweight z-score was positively associated with nearly all the outcomes (FFM, height, FFMI, FM and FMI) at 3 years of age. The strongest association was found between BWZ and FFM at 3 years with an increase of 380 g (95% CI: 122; 638) per one SD increase in
However, BWZ was likewise strongly associated with both FM and FMI. Per one SD increase in BWZ, FM at 3 years increased by 256 g (95% CI: 47; 465, \( p = 0.017 \)) and FMI at 3 years and 0.02 kg/m\(^2\) (95% CI: 0.0; 0.4, \( p = 0.034 \)).

Newborn FFM was positively associated with FFM, height and FFMI at 3 years with an increase of 100 g, 0.3 cm and 0.1 kg/m\(^2\), respectively, per every 100 g of newborn FFM (Table 3). Additionally, newborn FFM turned out to be positively associated with FM at
3 years with an increase of 58 g FM per every 100 g of newborn FFM (Table 4). Newborn total abdominal FFM was likewise positively associated with FFM and FFMI at 3 years and the association with height was borderline significant ($p=0.8$, 95% CI: $-0.1$; $1.7$, $p=0.064$). Per every 100 g of newborn total abdominal FFM, FFM at 3 years increased by 317 g (95% CI: 61; 572, $p=0.016$) and FFMI at 3 years increased by 0.2 kg/m$^2$ (95% CI: 0.1; 0.4, $p=0.012$; Table 3).

No significant associations were found between newborn FM, body fat in % or total abdominal FM and any of the outcomes at 3 years of age, although positive trends were seen between newborn FM and FM ($p=0.078$) and FM ($p=0.089$) at 3 years (Table 4).

4 | DISCUSSION

This study showed that infants who are born with a higher BWZ go on to be taller at 3 years. They also grow to be heavier, to which FM and FFM both contribute, and these associations persist independently of the increased linear growth. Moreover, we observed positive associations between FFM at birth and FFM and FFMI at 3 years, indicating a tracking of FFM throughout early life.

4.1 | Maternal and infants characteristics

The findings are based on measurements of infants born from obese mothers. It was shown that most of the mothers had an excessive weight gain during pregnancy (59%), which is in accordance with previous studies investigating pregnancy in obese mothers. Over half of the mothers (52%) had a medium education level or above. This in contrast to other studies that have linked maternal obesity to lower socioeconomic status and could be explained by the fact that it is often mothers with resources who participate in health-related studies.

When comparing feeding practices of the infants to recent data from the Danish Children’s Database, the duration of exclusive breastfeeding appears less than the average duration of full breastfeeding in the Capital Region of Denmark (3.9 months). Even though breastfeeding practices differ somewhat from the wider Danish population in the Capital Region, they appear consistent with practices observed in other studies investigating obese mothers.

While studies have linked maternal obesity and GWG to high birthweight in the offspring, it has also been associated with increased risk of delivering LGA infants. In this study, the majority (80%) were born AGA, whereas 18% were born LGA. The proportion of LGA infants is larger than expected, probably due to the participation of the mothers in the TOP intervention study.

### Table 2 Offspring body composition

<table>
<thead>
<tr>
<th>Included ($n=103$)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body composition at birth</strong></td>
<td></td>
</tr>
<tr>
<td>Fat-free mass (g)</td>
<td>3411 ± 391</td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td>400 (291–537)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>11.0 ± 4.5</td>
</tr>
<tr>
<td>Abdominal fat-free mass (g)</td>
<td>942 ± 131</td>
</tr>
<tr>
<td>Abdominal fat mass (g)</td>
<td>51 (33–73)</td>
</tr>
<tr>
<td><strong>Body composition at 3 years</strong></td>
<td></td>
</tr>
<tr>
<td>Fat-free mass (g)</td>
<td>12,585 ± 1180</td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td>2827 (2146–3396)</td>
</tr>
<tr>
<td>Fat-free mass index (kg/m$^2$)</td>
<td>13.0 ± 0.8</td>
</tr>
<tr>
<td>Fat mass index (kg/m$^2$)</td>
<td>2.9 (2.4–3.5)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>18.4 (15.5–21.6)</td>
</tr>
</tbody>
</table>

Note: Continuous data presented as mean ± SD if normally distributed and median (25th-75th percentiles) if not.

*Newborn body composition was addressed within 48h of birth by DXA.

### Table 3 Predictors of FFM, height and FFMI at 3 years of age

<table>
<thead>
<tr>
<th>Dependent variables at 3 years of age</th>
<th>FFM (g)</th>
<th>Height (cm)</th>
<th>FFMI (kg/m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight z-score (SD)$^a$</td>
<td>380 [122; 638]</td>
<td>1.0 [0.3;2.0]</td>
<td>0.2 [0.1;0.4]</td>
</tr>
<tr>
<td>FFM (g)$^bc$</td>
<td>100 [25;175]</td>
<td>0.3 [0.0;0.5]</td>
<td>0.1 [0.0;0.1]</td>
</tr>
<tr>
<td>FM (g)$^bc$</td>
<td>47 [−105;198]</td>
<td>0.542</td>
<td>0.03 [−0.1;0.1]</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>−10 [−86;66]</td>
<td>0.798</td>
<td>0.04 [−0.1;0.1]</td>
</tr>
<tr>
<td>Total abdominal FFM (g)$^bc$</td>
<td>317 [61;572]</td>
<td>0.8 [0.1;1.7]</td>
<td>0.2 [0.1;0.4]</td>
</tr>
<tr>
<td>Total abdominal FM (g)$^bc$</td>
<td>44 [−1017;1105]</td>
<td>0.934</td>
<td>0.002 [−0.7;0.7]</td>
</tr>
</tbody>
</table>

Abbreviations: FFM, fat-free mass; FM, fat mass; FFMI, fat-free mass index.

*Linear regression analysis adjusted for age at the 36 months of examination, maternal BMI at 9 months, gestational weight gain, total duration of breastfeeding, age of introduction to complementary feeding, maternal educational level, primiparity and maternal age.

*Linear regression analysis adjusted for the same as model$^a$, gestational age and sex.

*Results presented as per 100 g.

$P$-values ≤0.05 are marked with bold.
TABLE 4  Predictors of FM, body fat (%) and FMI at 3 years of age

<table>
<thead>
<tr>
<th>Newborn determinants</th>
<th>Dependent variables at 3 years of age</th>
<th>Body fat (%)</th>
<th>FMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FM (g)</td>
<td>β [95% CI] p</td>
<td>β [95% CI] p</td>
</tr>
<tr>
<td>Birthweight z-score (SD)</td>
<td>256 [47;465] 0.017</td>
<td>0.8 [-0.2;1.7] 0.131</td>
<td>0.2 [0.0;0.4] 0.034</td>
</tr>
<tr>
<td>FFM (g)</td>
<td>58 [1;114] 0.045</td>
<td>0.2 [-0.1;0.4] 0.228</td>
<td>0.1 [-0.0;0.1] 0.076</td>
</tr>
<tr>
<td>FM (g)</td>
<td>98 [-11;208] 0.078</td>
<td>0.4 [-0.1;0.9] 0.121</td>
<td>0.1 [-0.0;0.2] 0.089</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>34 [-21;89] 0.224</td>
<td>0.1 [-0.1;0.3] 0.231</td>
<td>0.03 [-0.0;0.1] 0.213</td>
</tr>
<tr>
<td>Total abdominal FFM (g)</td>
<td>180 [-12;373] 0.066</td>
<td>0.4 [-0.4;1.3] 0.323</td>
<td>0.2 [-0.0;0.3] 0.101</td>
</tr>
<tr>
<td>Total abdominal FM (g)</td>
<td>484 [-290;1259] 0.216</td>
<td>2 [-1;6] 0.230</td>
<td>0.5 [-0.3;0.2] 0.233</td>
</tr>
</tbody>
</table>

Abbreviations: FFM, fat-free mass; FM, fat mass; FMI, fat mass index.

Multiple regression analysis adjusted for age at the 36 months examination, maternal BMI at 9 months, gestational weight gain, total duration of breastfeeding, age of introduction to complementary feeding, maternal educational level, primiparity and maternal age.

Linear regression analysis adjusted for the same as model a, gestational age and sex.

Results presented as per 100g. P-values ≤0.05 are marked with bold.

4.2  Newborn body composition and anthropometry and body composition at 3 years

Our results implied that those infants who are born with a higher BWZ become taller and heavier in terms of both tissue compartments, such that adiposity measured as body fat in % is not increased. These findings are supported by the results from a very similar cohort study by Ejlerskov et al.19 who showed positive associations between BWZ and weight, height, BMI, FMI and FMI at 3 years of age (p ≤ 0.01) in Danish Children born from normal weight mothers.

We also showed a positive association between FFM at birth and FMI at 3 years of age. This association might be expected due to linear growth, as 100 g of higher FFM at birth was related to the children being 0.3 cm taller at 3 years (95% CI: 0.0; 0.5 p = 0.023). Though, when taking height into account as with FMI, the association was still significant, with an increase of 0.6 kg/m² (CI: 0.0; 0.1, p = 0.014) per every 100 g of newborn FFM, indicating that FFM at birth is associated with FMI at 3 years beyond that explained by linear growth. As such, intrauterine programming of later health may be supported, as newborn FFM is tracked into early childhood.6 As the majority of studies investigating associations between newborn and later body composition have focused on body composition within the first year of life,22-24 it is difficult to say whether the current results are consistent with the literature. However, in the study by Forsum et al.6 they showed that FFM and FMI at 1 and 12 weeks were positively associated with FFM and FMI at 4 years (p < 0.002) in 253 Swedish children. By the use of ADP, similar associations were found by Admassu et al.4 They reported that 1 kg higher FFM at birth was related to 1.07 kg/m² higher FMI in children aged 4 years (p < 0.001).4 However, this study was conducted in Jimma, Ethiopia, and several studies have demonstrated differences in offspring body composition in relation to ethnicity, which complicates the comparison of results between countries of high and low income.22,25

Reference data on body composition in different populations are therefore of high interest, and comparisons between ethnicities should be done so with caution. Another interesting finding in this study was that newborn FFM turned out to be associated with FM but not with FMI at 3 years (β = 57.76, 95% CI: 1.3; 114.2, p = 0.045). Therefore, it seems like a greater FFM in infancy results in greater FMI in early childhood, which is further accompanied by an appropriate accretion of FM for the size of the child.

Lastly, no associations were found between FM, body fat in % and abdominal FM at birth and anthropometry and body composition at 3 years. This is in contrast to the findings from other studies.4-6 For instance, Forsum et al.6 showed that FM, FMI and body fat in % at 12 weeks were positively associated with FM, FMI and body fat in % at 4 years of age (P ≤ 0.04). Similarly, Admassu et al.4 found a positive linear relationship between FM at birth and FMI at 4 years of age in their Ethiopian cohort. Moreover, van Beijsterveldt et al. reported that body fat in % and FM tracked from age 3 and 6 months to 4 years in 224 children from Dutch birth cohort, thus supporting adiposity programming by the use of ADP and DXA scans.26 Among the infants in our study, we did not find evidence of tracking of FM, although we found positive trends between FM at birth and FM and FMI at 3 years of age. This could indicate a genuine difference in tracking, but may be explained by a larger range of FM among included children, as studies have shown that FM is more readily influenced by environmental factors than FFM.9 To further confirm if our findings are consistent, future research is needed within the area of total and regional body composition during infancy and childhood.

4.3  Strengths and limitations

Our study is based on data from a large prospective cohort, which made it possible to follow participants longitudinally and collect a wide range of data of potential confounders. Additionally, it is unique that

the analysis includes data on newborn body composition measured by DXA, as it is rarely performed due to practicalities and financial reasons. It should be noted that no causal relationship can be drawn and we cannot rule out residual confounding related to maternal obesity, diet and other lifestyle factors. Moreover, these results are from obese mothers only and might therefore not be applicable to the general population, hence lowering the external validity.

The infants in this study were recruited from the TOP intervention study which aimed to restrict GWG. However, the intervention did not affect birthweight or newborn body composition, which is why the TOP intervention was not adjusted for in our analysis. Maternal participation in the TOP study could likewise decrease the generalisability and affect the results, underestimating the effect of maternal obesity, since offspring body composition might be different in children born from mothers with lower resources and less awareness of a healthy lifestyle.

In our study, different techniques were used to obtain data on body composition. At birth, body composition was measured by DXA scans. Even though DXA is a highly reliable method when measuring infant body composition, it is limited by factors such as movement during scanning, infant milk intake and the high cost of the machine. To test the variability of the DXA scans included in our study, 58 infants were scanned twice. The results showed that the variability was 11.8% for newborn FM and 7.1% for newborn FFM. At 3 years, body composition was estimated by BIA and predictive equations, generated from DXA scans in 99 3-year-old Danish children. The prediction errors for FM and FFM were 10.5% and 3.0% with mean differences between BIA and DXA values of −6 and −4 g, respectively. Due to the high agreement, we believe it is acceptable to compare newborn body composition estimates obtained from DXA scans with estimates at 3 years derived from BIA in this study. However, it should be noted that several factors are found to limit the use of BIA, especially in paediatric populations. For instance, the method assumes a constant tissue hydration, which is changing with age, size, temperature and physical activity. Moreover, it can be difficult to maintain the child in a still and supine position for the required period. Finally, the prediction errors associated with BIA may reduce confidence in our findings given the modest associations and should be considered for interpretation. This error is not uncommon in studies utilising BIA as a method of body composition assessment, but a high degree of standardisation should be maintained in order to compare data between studies investigating paediatric populations and make appropriate inferences. Despite the limitations, the BIA method was chosen, as predictive equations were available for a very similar population, which we believe strengthens the validity of the results.

5 CONCLUSION

This study showed that infants who are born with a higher BWZ go on to be taller at 3 years. They also grow to be heavier, to which FM and FFM both contribute, and these associations persist independently of the increased linear growth. In addition, it showed that FFM tracks into early childhood, thus supporting intrauterine programming of later health. Associations between newborn FM and FM at 3 years remain inconclusive. Finally, more research is needed to confirm the tracking of body composition from infancy through childhood and to understand potential underlying mechanisms. Following birth cohorts throughout infancy, childhood and beyond will support the investigation of infant body composition and its impact on later health.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

ORCID

Nanna R. Berglund https://orcid.org/0000-0002-8325-1029

Jack I. Lewis https://orcid.org/0000-0001-9483-912X

REFERENCES


SUPPORTING INFORMATION

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