Early rapid growth: no association with later cognitive functions in children born not small for gestational age\textsuperscript{1–3}

Andreas Beyerlein, Andrew R Ness, Ina Streuling, Mijna Hadders-Algra, and Rüdiger von Kries

ABSTRACT

Background: There is an association between rapid growth in early life and overweight in childhood. This adverse association needs to be balanced against potential beneficial effects on cognitive functioning observed in children who are born small for gestational age (SGA).

Objective: We examined potential beneficial effects of rapid growth on cognitive functions in non-SGA children.

Design: We performed a systematic literature search of 3 databases. In addition, we analyzed data from the Avon Longitudinal Study on Parents and Children (ALSPAC). The association of rapid weight or length gain (defined as an increase of \(>0.67\) in the SD score of weight or length between birth and the age of 25 mo) on intelligence quotient (IQ) measurements at 49 mo and 8 y (n = 836 and n = 701, respectively) was assessed in linear models adjusted for potential confounders.

Results: We identified 14 studies that assessed associations between any kind of early weight gain and cognitive outcome and that included non-SGA children. No study explicitly examined the effect of rapid weight gain. In the ALSPAC data, there was no positive association between rapid weight gain and IQ scores at either 49 mo or 8 y, whereas rapid length gain was positively associated with IQ at 8 y. In subgroup analyses with stratification by sex of the children, IQ scores were higher in boys but lower in girls for rapid weight gain. Supplementary analyses showed no linear association between weight gain and IQ.

Conclusion: We showed no evidence that proposed adverse effects of rapid growth regarding later overweight will be counterbalanced by beneficial effects on cognitive functions in non-SGA children.

INTRODUCTION

There is strong evidence that rapid growth in early infancy, either defined as length or weight gain, is a predictor of later overweight (1–4). However, it appears to be associated with improved neurodevelopment and cognitive functioning in low birth weight or small-for-gestational-age (SGA) infants (5–10) or preterm children (11–14).

Few studies have assessed the effect of any kind of early weight gain on cognitive outcome in children born appropriate for gestational age or large for gestational age, and to our knowledge, no study explicitly assessed the association of rapid growth on cognitive outcome in non-SGA children.

Because rapid growth—in most cases defined by weight gain (1)—has consistently been shown to be a risk factor for overweight in childhood, a positive association with the later intelligence quotient (IQ) in non-SGA children would be highly relevant with respect to possible policy recommendations, particularly because nutritional strategies appear to be successful in enhancing (15–18) or reducing (19) early growth.

The objective of this article was to assess whether the established adverse association of rapid growth with respect to later overweight might be counterbalanced by benefits in cognitive function in non-SGA children. We carried out a systematic literature search to identify relevant studies on this topic. Furthermore, we used data from the prospective Avon Longitudinal Study on Parents and Children (ALSPAC) because these have previously been analyzed with respect to associations of rapid weight gain on later overweight and yielded a widely quoted article (2). Because the ALSPAC study also provides data on IQ measurements at 49 mo and 8 y, we used these data to assess potential effects of rapid weight or length gain on cognitive function.

SUBJECTS AND METHODS

To identify the relevant literature, we searched the databases MEDLINE (1950–2010; www.ncbi.nlm.nih.gov/pubmed), PSYCHINFO (1800–2010; www.apa.org/pubs/databases/psychinfo/index.aspx), and Web of Science (1900–2010; www.isiknowledge.com) by using the keywords (“Child” OR “Infant” OR “Childhood”) AND (“weight gain” OR “weight growth” OR “catch-up growth”) AND (“cognitive development” OR “mental processes” OR “mental disorders” OR “developmental disabilities”)

\textsuperscript{1} From the Institute of Social Pediatrics and Adolescent Medicine, Division of Epidemiology, Ludwig-Maximilians University of Munich, Munich, Germany (AB, IS, and RvK); the Department of Oral and Dental Science, University of Bristol, Bristol, United Kingdom (ARN); and the Department of Paediatrics, Division of Developmental Neurology, University Medical Center Groningen, Groningen, Netherlands (MH-A).

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\textsuperscript{3} Address correspondence to A Beyerlein, Institute for Social Pediatrics and Adolescent Medicine, Division of Epidemiology, Ludwig-Maximilians University of Munich, Heiglofsstr 63, 81377 Munich, Germany. E-mail: andreas.beyerlein@med.uni-muenchen.de.

OR “executive function” OR “IQ”). The electronic literature search was carried out in February 2010. An additional hand search of reference lists of relevant and related articles was made to ensure a complete collection. We included all studies that reported any associations between weight gain from birth to the age of ≤2 y and neurodevelopment or cognitive functions at any age in studies that included non-SGA children. The search method was conducted in keeping with the review of Ong et al (3) who had searched for studies that assessed effects of rapid weight gain from birth to ≤2 y on later overweight. Furthermore, the most dramatic neuro-developmental changes after birth occur during the first 2 postnatal years. The articles were screened by their titles, and inappropriate topics were excluded. Two researchers (IS and AB) independently analyzed and selected the identified abstracts and full-text articles according to the inclusion criteria. We assessed the quality of the individual studies according to criteria published in the International Journal of Epidemiology (20). The systematic review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (www.prisma-statement.org).

The ALSPAC is a longitudinal birth cohort study of the determinants of development, health, and disease during childhood and beyond. Initially, 14,541 pregnant women with an expected date of delivery between April 1991 and December 1992 were enrolled; 13,971 of their children formed the original cohort at 1 y of age. The study is described in more detail elsewhere (21).

At regular intervals from birth to adolescence of the children, questionnaires containing lifestyle and child-related questions were sent to parents of all registered children. A random sample of ≈10% (n = 1322) of the children was invited [of which n = 1127 (85%) appeared] to examinations and measurements of standing height and weight at regular time points during the first 5 y of life with the Leicester height measure (Child Growth Foundation, London, United Kingdom) and Seca 724 or 835 scales (Seca, Hamburg, Germany), respectively.

At the ages of 49 mo and 8 y, children’s cognitive functioning was measured by Wechsler Preschool and Primary Scale of Intelligence (WPPSI) tests and Wechsler Intelligence Scale for Children III (WISC-III) tests (22, 23), respectively. The Wechsler tests are the most used individual ability tests worldwide. They are standardized to a mean (± SD) of 100 ± 15 points. The WPPSI and WISC-III comprise 10 subtests (5 verbal and 5 performance subtests) that sum to the verbal IQ and performance IQ. The 10 subtest scores combine to produce a full-scale IQ. For example, the WISC-III consists of subtests on information, similarities, arithmetic skills, vocabulary, comprehension (all verbal), picture completion, coding, picture arrangement, block design, and object assembly (all performance). All tests were administered by the ALSPAC psychology team. We considered a difference of >3.5 IQ points between groups as clinically relevant, which corresponded with the SEs of measurement of the WPPSI (3.67) and the WISC-III (between 3.53 and 4.58 on different subscales).

We calculated SD scores (SDS) of weight and length on the basis of the British growth reference centiles from 1990 (24) with Excel macros provided on the Internet (www.healthforallchildren.co.uk). We defined SGA by an SDS of weight at birth below −1.28 (10th percentile of the normal distribution).

Rapid weight gain was defined as an increase of >0.67 in the SDS of weight between birth and the age of 25 mo (binary variable) because this was the most frequent definition of rapid growth used in previous publications (3). Ong et al (2) used the same definition in their previous study in the ALSPAC children that assessed the association of rapid weight gain on childhood overweight, but their calculations were based on sample-specific SDS (2, 25) rather than external reference scores. In a sensitivity analysis, we replaced our rapid weight gain variable by that of Ong et al (2, 25) to explore potential differences between analyses of Ong et al (2, 25) and our analyses because of the definition of rapid weight gain. Accordingly, we defined rapid length gain as an increase of >0.67 in the SDS of length between birth and the age of 25 mo.

Breastfeeding and maternal smoking were coded as 2 categories (ie, ever and never). We also coded maternal education

![Diagram](https://via.placeholder.com/150)

**FIGURE 1.** Flow diagram of children analyzed in the Avon Longitudinal Study on Parents and Children data set. IQ, intelligence quotient; SGA, small-for-gestational-age. *Breastfeeding, maternal age, maternal education, maternal smoking (ever).
### Table 1

Studies that included non–small-for-gestational-age children and assessed failure to thrive (FTT) or poor weight gain (WG) to explain cognitive outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population and years</th>
<th>n</th>
<th>Definition of FTT</th>
<th>Effect of FTT</th>
<th>AC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glaser et al, 1968 (34)</td>
<td>United States 1958–1965</td>
<td>40</td>
<td>Weight less than third percentile at hospitalization</td>
<td>IQ scores at follow-up “approximated a normal distribution with a skewing to the left”</td>
<td>—</td>
<td>Hospitalization at age &lt;6 to &gt;18 mo; follow-up at ages of 8 mo to 8 y</td>
</tr>
<tr>
<td>Hack et al, 1982 (6)</td>
<td>United States 1977–1978</td>
<td>192</td>
<td>Weight SDS less than −2 at term and at 8 mo</td>
<td>Lower MDI at 8 mo (P &lt; 0.005)</td>
<td>—</td>
<td>154 children classified as AGA (birth weight SDS of at least −2)</td>
</tr>
<tr>
<td>Wilensky et al, 1996 (38)</td>
<td>Israel 1991</td>
<td>100</td>
<td>Weight less than third percentile for ≥3 mo</td>
<td>Lower MDI at 20 mo (P &lt; 0.05)</td>
<td>ADFIKL</td>
<td>Matched pairs</td>
</tr>
<tr>
<td>Drewett et al, 2001 (31)</td>
<td>Ethiopia 1992–1993</td>
<td>914</td>
<td>Early growth faltering: weight at 2 or 4 mo less than third percentile; late growth faltering: weight at 10 and 12 mo but not at 2 or 4 mo less than third percentile</td>
<td>Less MDI items passed in early growth faltering group (P = 0.13); almost no differences in late growth faltering compared with control subjects (P = 0.78)</td>
<td>JLM</td>
<td>Initial weights were available for all children ≤16 d of age; 80% were recorded by day 4</td>
</tr>
<tr>
<td>Latal-Hajnal et al, 2003 (7)</td>
<td>Switzerland 1983–1994</td>
<td>219</td>
<td>Weight at 2 y &lt;10th percentile</td>
<td>Lower MDI at 2 y in AGA children (P &lt; 0.05)</td>
<td>—</td>
<td>125 children classified as AGA (&gt;10th gestational-age-specific birth weight percentile)</td>
</tr>
<tr>
<td>Casey et al, 2006 (12)</td>
<td>United States 1984–1985</td>
<td>544</td>
<td>Weight less than fifth percentile at ≥2 points in time (measured at 4, 8, 12, 18, 24, 30 and 36 mo gestational corrected age)</td>
<td>Lower IQ at 8 y (P &lt; 0.05)</td>
<td>ADGIL</td>
<td>—</td>
</tr>
<tr>
<td>Black et al, 2007 (29)</td>
<td>United States 1989–1992</td>
<td>189</td>
<td>Sustained weight-for-age less than fifth percentile or weight-for-length &lt;10th percentile at age &lt;25 mo</td>
<td>Almost equal cognitive or academic performance at 8 y between FTT children and children with adequate growth</td>
<td>J</td>
<td>—</td>
</tr>
<tr>
<td>Emond et al, 2007 (32)</td>
<td>United Kingdom 1991–1992 (ALSPAC)</td>
<td>5771</td>
<td>Difference in weight SDS less than −1.645 (fifth percentile) from birth to 8 wk and from birth to 9 mo</td>
<td>Poor WG ≤8 wk; lower IQ levels at 8 y (P = 0.11); poor WG ≤9 mo; lower IQ levels at 8 y (P = 0.008)</td>
<td>BFGIM</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>1</sup> AC, adjustment for confounders; IQ, intelligence quotient; SDS, SD score; MDI, Mental Developmental Index of Bayley Scales (39); AGA, appropriate for gestational age.

<sup>2</sup> Adjusted for birth weight (A), breastfeeding (B), current age (C), ethnicity (D), gestational age (E), maternal age (F), maternal height (G), maternal smoking (H), multiple delivery (I), parental education or IQ (J), parity (K), sex (L), and socioeconomic status (M) (the list contains only confounders that were used in ≥2 studies).
<table>
<thead>
<tr>
<th>Study</th>
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<th>Definition of WG</th>
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<th>AC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latal-Hajnal et al, 2003 (7)</td>
<td>Switzerland 1983–1994</td>
<td>219</td>
<td>WG from birth to 2 y</td>
<td>Small positive correlation ($P &gt; 0.05$) with MDI at 2 y</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Corbett et al, 2007 (30)</td>
<td>United Kingdom 1987–1988</td>
<td>1792</td>
<td>Difference in weight SDS from birth to latest available measurement</td>
<td>Positive relations with reading scores ($P = 0.10$), math scores ($P = 0.12$), problems of position ($P = 0.22$), and picture vocabulary ($P = 0.003$) at 10 y</td>
<td>E</td>
<td>Latest available measurements at 9–24 mo</td>
</tr>
<tr>
<td>Emond et al, 2007 (32)</td>
<td>United Kingdom 1991–1992 (ALSPAC)</td>
<td>5771</td>
<td>Difference in weight SDS from birth to 8 wk and from birth to 9 mo</td>
<td>WG $\leq$ 8 wk: linear relation to IQ at 8 y ($P = 0.0002$); WG $\leq$ 9 mo: weak positive association with IQ at 8 y ($P = 0.36$)</td>
<td>BFGJM</td>
<td>—</td>
</tr>
<tr>
<td>Belfort et al, 2008 (28)</td>
<td>United States 1999–2003</td>
<td>872</td>
<td>Difference in weight SDS from birth to 6 mo</td>
<td>No effect on PPVT-III (40) and WRAVMA (41) scores at 3 y ($P &gt; 0.05$)</td>
<td>CDFHJKLM</td>
<td>—</td>
</tr>
<tr>
<td>Heinonen et al, 2008 (35)</td>
<td>Finland 1985–1986</td>
<td>1056</td>
<td>Difference in weight SDS from birth to 5 mo</td>
<td>Positive effects on general reasoning ($P &lt; 0.01$), visual motor integration and functioning ($P &lt; 0.001$), verbal competence ($P &gt; 0.05$), and language comprehension ($P &gt; 0.05$)</td>
<td>BEFHJL</td>
<td>—</td>
</tr>
<tr>
<td>Estourgie-van Burk et al, 2009 (33)</td>
<td>Netherlands Twin Register</td>
<td>308</td>
<td>(154 pairs) Difference in weight SDS from birth to 2 y</td>
<td>Negative correlation with IQ at 12 y ($P = 0.02$) and 18 y ($P = 0.01$)</td>
<td>—</td>
<td>Twin study; confounding by low birth weight likely</td>
</tr>
<tr>
<td>Räkkönen et al, 2009 (37)</td>
<td>Finland 1952–1972</td>
<td>2786</td>
<td>Difference in weight SDS from birth to 2 y</td>
<td>Positive associations with verbal reasoning ($P &gt; 0.05$), visuospatial reasoning ($P &lt; 0.05$), and arithmetic reasoning ($P &gt; 0.05$)</td>
<td>BCFGKM</td>
<td>Participants born in 1934–1944</td>
</tr>
<tr>
<td>Martorell et al, 2010 (36)</td>
<td>India, Brazil, Guatemala, Philippines, South Africa 1969–1990</td>
<td>7945</td>
<td>Difference in weight SDS from birth to 2 y</td>
<td>Positive effect on highest school grade attained ($P &lt; 0.0001$)</td>
<td>JLM</td>
<td>Cohorts recruited at different time points</td>
</tr>
</tbody>
</table>

<sup>1</sup> AC, adjustment for confounders; MDI, Mental Developmental Index of Bayley Scales (39); SDS, SD score; IQ, intelligence quotient; PPVT-III, Peabody Picture Vocabulary Test—third edition; WRAVMA, wide range of visual motor abilities; ALSPAC, Avon Longitudinal Study on Parents and Children.

<sup>2</sup> Adjusted for birth weight (A), breastfeeding (B), current age (C), ethnicity (D), gestational age (E), maternal age (F), maternal height (G), maternal smoking (H), multiple delivery (I), parental education or IQ (J), parity (K), sex (L), and socioeconomic status (M) (the list contains only confounders that were used in $\geq 2$ studies).
In further supplementary analyses, we explored the effect of weight gain as a continuous predictor variable (i.e., weight gain SDS). First, we used weight gain SDS as a linear predictor variable. In addition, we assessed potential nonlinear effects by modeling weight gain by cubic splines with \( \leq 3 \) df (26). Model selection was performed with the Akaike information criterion (27).

Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees. All calculations were carried out with the open-source software R (version 2.6.2; R Foundation for Statistical Computing, Vienna, Austria).

### RESULTS

We screened the titles of 1542 articles that were identified by the literature search and excluded all studies that evidently did not report the growth or intellectual performance of infants. The remaining 116 abstracts were scrutinized. Reviews and studies on a different topic were excluded. A total of 26 studies were potentially relevant for full text investigation. Of these, we identified 14 studies (6, 7, 12, 28–38) that assessed associations between early weight gain or loss (in terms of weight SDS) from birth to \( \leq 2 \) y and cognitive outcome that included non-SGA children (Figure 1). Compared with the children analyzed (i.e., the combined SGA and non-SGA group), the term-born children excluded from the 10% random sample because of missing information on covariates were not significantly (\( P < 0.05 \)) different in proportions of SGA (11.6% compared with 8.0%; \( P = 0.15 \)) and rapid weight gain (34.2% compared with 31.2%; \( P = 0.43 \)) and had lower mean (95% CI) IQ scores at 49 mo (99.5 (97.4, 101.6) compared with 103.7 (103.0, 107.0); \( P = 0.03 \)).

Mean differences in IQ scores were calculated with 95% CIs unadjusted and adjusted for confounders. This was done by applying multivariable linear models with IQ scores as outcome variables, rapid weight gain as an explanatory variable, and sex, breastfeeding, and maternal age, education, and smoking as potential confounding variables (as derived from a priori considerations). Models were calculated for all children and additionally stratified for SGA and non-SGA children as well as for sex. We repeated these analyses with rapid weight instead of weight gain (with 1022 children with complete information on length gain from birth to 25 mo). To explore potential bias by confinement of our main analyses to complete cases, we repeated the unadjusted analyses on the data of non-SGA children with full measurements on weight gain and IQ at 49 mo (\( n = 823 \)) or 8 y (\( n = 680 \)), irrespective of available information on potential confounders.
considerably more likely to show rapid weight and length gain. All children (Tables 1 and 2) (see supplemental figure under “Supplemental data” in the online issue for a flowchart of included studies). One study was also based on the ALSPAC data set but did not distinguish between SGA and non-SGA children (32). Two studies allowed for conclusions on both poor weight gain and total weight gain (7, 32). Ten studies had adjusted for potential confounders, such as sex, maternal age, or parental education (12, 28–32, 35–37). All confounders that were assessed in more than one study are listed in Tables 1 and 2. Several confounders appeared in single studies such as the number of possessions (31) or receipt of public assistance (29) and, therefore, seemed to be relatively study specific so that we decided not to add them to the list in Tables 1 and 2 (see supplemental table under “Supplemental data” in the online issue for a quality assessment of the individual studies).

Seven studies suggested detrimental associations between poor growth and cognitive outcome (6, 7, 12, 31, 32, 34, 38). However, 3 of these studies (6, 7, 34) did not adjust for potential confounders, whereas children with and without failure to thrive showed almost similar mean IQ levels in another study (29).

The effects of early weight gain as a continuous variable on cognitive functioning were largely consistent (Table 2): 6 studies detected potential positive effects on cognitive functioning (7, 30, 32, 35–37), and only one study showed no association (28). A twin study detected a negative association, but the association was likely confounded by low birth weight (33). In one study, weight gain in the first 8 wk was positively associated with later IQ but weight gain in the first 9 mo was not (32).

Descriptive statistics of SGA and non-SGA children in the ALSPAC data set examined are given in Table 3. Overall, mean (±SD) values of SDS of birth weight and weight at 25 mo were 0.0 ± 1.0 and 0.2 ± 1.0, respectively. SGA children were considerably more likely to show rapid weight and length gain than non-SGA children (P < 0.01 each).

In linear regression models with adjustment for potential confounders, rapid weight gain in the first 2 y was not positively associated with IQ scores at 49 mo in non-SGA children and showed an effect estimate of −1.4 (−3.6, 0.7) (P = 0.18; Table 4). Similarly, no positive association was observed for IQ measurements at 8 y in non-SGA children [−0.8 (−3.4, 1.9); P = 0.58; Table 5]. There were also no significantly positive associations shown in SGA children for IQ at 49 mo [4.7 (−2.5, 11.9); P = 0.19] and 8 y [2.7 (−8.0, 13.5); P = 0.51]. In the full data set that included SGA and, predominantly, non-SGA children, the observed associations were close to zero. Most of the adjusted effect estimates differed by ≤1.0 IQ points from the unadjusted ones, which suggested that confounding was not a major issue in the respective models (Table 5). Differences of >1.0 in IQ scores between unadjusted and adjusted estimates occurred almost exclusively in SGA children. The unadjusted estimates in non-SGA children without complete information on covariates were similar to those from the main unadjusted analyses (data not shown).

Post hoc subgroup analyses showed no clear sex-specific associations of rapid weight gain with IQ measurements at 49 mo and 8 y in either SGA or non-SGA children (Table 5). Sensitivity analyses with rapid weight gain as calculated in Ong et al (2, 25) led to similar results (data not shown).

In non-SGA children, an increase of one unit in weight gain SDS was associated with an increase of 0.1 (−0.8, 1.1) units in IQ at 49 mo and of 0.2 (−1.0, 1.4) units in IQ at 8 y (adjusted analyses). In SGA children, the corresponding linear regression

<p>| TABLE 5 | Regression coefficients (95% CIs) of rapid weight gain (first 25 mo of life) in linear models with intelligence quotient (IQ) measurements at 49 mo and 8 y as outcome variables, unadjusted and adjusted for the potential confounders sex, breastfeeding, maternal age, maternal education, and maternal smoking. |
|-----------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children</td>
<td>−0.9 (−3.0, 1.2)</td>
<td>−1.1 (−3.1, 0.8)</td>
<td>−0.2 (−2.8, 2.4)</td>
<td>−0.7 (−3.2, 1.8)</td>
</tr>
<tr>
<td>R²</td>
<td>0.00</td>
<td>0.12</td>
<td>0.00</td>
<td>0.08</td>
</tr>
<tr>
<td>Males</td>
<td>−0.5 (−3.2, 2.4)</td>
<td>−1.1 (−3.8, 1.6)</td>
<td>−1.3 (−5.0, 2.4)</td>
<td>−2.4 (−6.0, 1.2)</td>
</tr>
<tr>
<td>R²</td>
<td>0.00</td>
<td>0.13</td>
<td>0.00</td>
<td>0.07</td>
</tr>
<tr>
<td>Females</td>
<td>−1.5 (−4.5, 1.5)</td>
<td>−1.2 (−4.2, 1.3)</td>
<td>1.1 (−2.5, 4.6)</td>
<td>1.2 (−2.2, 4.6)</td>
</tr>
<tr>
<td>R²</td>
<td>0.11</td>
<td>0.01</td>
<td>0.00</td>
<td>0.13</td>
</tr>
<tr>
<td>Non-SGA</td>
<td>−1.1 (−3.4, 1.1)</td>
<td>−1.4 (−3.6, 0.7)</td>
<td>−0.1 (−2.9, 2.6)</td>
<td>−0.8 (−3.4, 1.9)</td>
</tr>
<tr>
<td>R²</td>
<td>0.00</td>
<td>0.12</td>
<td>0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Males</td>
<td>−0.9 (−4.1, 2.2)</td>
<td>−1.7 (−4.6, 1.5)</td>
<td>−1.4 (−5.3, 2.6)</td>
<td>−2.6 (−6.5, 1.3)</td>
</tr>
<tr>
<td>R²</td>
<td>0.00</td>
<td>0.12</td>
<td>0.00</td>
<td>0.07</td>
</tr>
<tr>
<td>Females</td>
<td>−1.4 (−4.6, 1.8)</td>
<td>−1.3 (−4.3, 1.8)</td>
<td>1.3 (−2.5, 5.1)</td>
<td>1.3 (−2.3, 5.0)</td>
</tr>
<tr>
<td>R²</td>
<td>0.00</td>
<td>0.12</td>
<td>0.00</td>
<td>0.13</td>
</tr>
<tr>
<td>SGA</td>
<td>3.3 (−3.9, 10.5)</td>
<td>4.7 (−2.5, 11.9)</td>
<td>0.9 (−9.3, 11.2)</td>
<td>2.7 (−8.0, 13.5)</td>
</tr>
<tr>
<td>R²</td>
<td>0.01</td>
<td>0.21</td>
<td>0.00</td>
<td>0.13</td>
</tr>
<tr>
<td>Males</td>
<td>5.4 (−3.7, 14.5)</td>
<td>5.6 (−2.7, 13.9)</td>
<td>0.3 (−13.7, 14.2)</td>
<td>1.6 (−13.0, 16.3)</td>
</tr>
<tr>
<td>R²</td>
<td>0.04</td>
<td>0.35</td>
<td>0.00</td>
<td>0.17</td>
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<tr>
<td>Females</td>
<td>−1.8 (−14.5, 10.9)</td>
<td>2.5 (−15.2, 20.5)</td>
<td>2.2 (−14.6, 19.1)</td>
<td>3.2 (−16.9, 23.3)</td>
</tr>
<tr>
<td>R²</td>
<td>0.00</td>
<td>0.07</td>
<td>0.00</td>
<td>0.10</td>
</tr>
</tbody>
</table>

1 n in brackets. SGA, small for gestational age.
coefficients for IQ at 49 mo and 8 y were 1.3 (−1.5, 4.2) and 3.5 (−0.5, 7.6), respectively.
Analyses with weight gain as a nonlinear predictor variable confirmed that rapid weight gain (ie, high values of weight gain SDS) was not associated with a higher IQ in non-SGA children (Figure 2) as derived from the values of the effect estimates and their associated 95% confidence bands. In SGA children, there seemed to be a rather linear positive relation between weight gain (from −1 to up to +2 units of SDS) and later IQ, whereas weight gain >2 SDS did not appear to convey further benefits.

DISCUSSION
No evidence was obtained from both the systematic literature review and analyses of a cohort of considerable size that adverse effects of rapid growth regarding later overweight will be counterbalanced by beneficial effects on cognitive functions in non-SGA children. Although previous studies did not address this issue appropriately, our own analyses suggest no relevant associations between rapid weight gain in the first 2 y of life and cognitive functioning later in childhood.

Literature review
Our systematic literature search yielded only studies that addressed either poor weight gain or weight gain as a linear or multicategorical variable in data that included non-SGA children. Seven out of 8 studies (6, 7, 12, 31, 32, 34, 38) that assessed poor weight gain showed associations with lower IQ. However, 3 of these studies (6, 7, 34) were not adjusted for potential confounders, which potentially limited their validity. Confounders such as, eg, breastfeeding, social class, or maternal smoking were considered in 4 studies (12, 31, 32, 38). However, only one of the studies (29) used the Home Observation for Measurement of the Environment (HOME) scores (42) to adjust for a neglectful environment that may contribute to poor growth and cognitive delays as a result of a lack of stimulation. Therefore, although an association between weight loss in early life and poor intellectual development appears possible, the empirical evidence is not conclusive.

With the exception of the results of a twin study (33), which might have been heavily confounded by effects of low birth weight, the results of the individual studies by using weight gain as a continuous or multicategorical variable were widely consistent independent of adjustment for confounding factors, and most of the studies (7, 30, 32, 35–37) showed weak positive associations between weight gain and cognitive development. However, these associations might rather be due to potential detrimental effects of slow weight gain on cognitive development that account for spurious linear associations.

Therefore, neither of the approaches that considered either poor or weight gain as a continuous variable allow for identification of a specific effect of high compared with normal weight gain on IQ in non-SGA children. None of the identified studies assessed the effect of early rapid weight gain on later cognitive outcome in non-SGA children explicitly with reference to normal weight gain.

In summary, there are some data that suggest a detrimental effect of poor weight gain on cognitive functioning. Because an adverse effect of poor weight gain might underlie the observed linear associations between weight gain and cognitive
functioning, there was a need to assess the potential effect of rapid weight gain on IQ development.

Results from the ALSPAC data set

A previous study on the basis of the ALSPAC data showed an adverse association of very slow weight gain in the first 9 mo on later IQ but showed no association with rapid weight gain (32). However, this study did not distinguish between SGA and non-SGA children.

Our own analyses on the ALSPAC data showed that rapid growth in the first 2 y of life, a risk factor for later overweight, was not associated with cognitive functioning at 49 mo or 8 y in non-SGA children. The lack of association in non-SGA children is unlikely to be due to a lack of statistical power: With consideration of the 95% CIs of the regression estimates for the effect of rapid weight gain on IQ measurements at 49 mo and 8 y (upper limits: 0.7 and 1.9, respectively), it appears unlikely that we missed positive associations of >2 IQ units. In comparison, effect sizes of 3.2 and 5 IQ points were reported for breastfeeding (compared with bottle feeding) or normal compared with low birth weight (<2500 g) in systematic reviews (43, 44).

In contrast, in SGA children a linear positive relation between weight gain and later IQ appears possible on the basis of our results, although the number of SGA children was too small to draw final conclusions for this subgroup.

Implications

Our data suggest that there might be different biological implications of rapid weight gain in SGA and non-SGA children. In SGA children rapid weight gain probably reflects catch-up growth, which brings these children to a normal weight level. Catch-up growth is a common physiologic reaction to low birth weight, which explains why, as in our study, rapid weight gain is much more frequently observed in SGA compared with non-SGA children (45). In previous studies with larger samples, rapid weight gain was shown to be positively associated with IQ in SGA children (5, 9, 10). In general, our results were in keeping with these findings, although there were too few SGA children in our data set to draw final conclusions with respect to this subgroup. In contrast, there is no evident reason to assume that rapid weight gain in non-SGA children is a physiologic reaction, and there is no evidence for a beneficial effect with respect to intellectual development.

Subgroup analyses

We observed no clear evidence for sex-specific effects in either non-SGA or SGA children, although some of the effect estimates of rapid weight gain differed to some extent between male and female children in stratified analyses (Table 5). In general, positive findings from subgroup analyses need to be interpreted with care because there is a high risk of spurious findings because of multiple testing.

Strengths and limitations

The prospective design of the ALSPAC data set constitutes a strength of our main analyses because reverse causation is not likely to be an issue. A bias from confinement of our main analyses to children with complete data on confounding factors is unlikely from supplementary analyses.

Unfortunately, we were not able to analyze the full ALSPAC data set because measurements on early weight gain were only available for a 10% random sample, which limited the statistical power of our study. With a greater sample size, even smaller differences in IQ between groups with and without rapid weight gain might be detectable, but the statistical power of our study was sufficient to detect effects in the size of the SEs of the IQ measurements taken.

A further potential limitation pertains to the exclusion of nonsingleton and preterm deliveries, which may limit the generalizability of our study findings with respect to these subgroups. However, our study, like that of Ong et al (2) on the relation of rapid weight gain and childhood overweight, focuses on term singletons and, therefore, on the majority of infants.

Conclusions

In conclusion, our results indicate that adverse effects of rapid weight gain regarding later overweight are not counterbalanced by beneficial effects on cognitive functioning in non-SGA children, whereas rapid weight gain might be beneficial for SGA children because of potential benefits on intellectual development, as shown in other studies.

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REFERENCES

9. Pylipow M, Spector LG, Puumala SE, Boys C, Cohen J, Georgi eff MK. Early postnatal weight gain, intellectual performance, and body mass...