Very Low Birth Weight, Infant Growth, and Autism-Spectrum Traits in Adulthood

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KEY WORDS
autism-spectrum, preterm birth, very low birth weight, infant growth

ABBREVIATIONS
AGA—appropriate for gestational age
AQ—The Autism-Spectrum Quotient
ASD—autism-spectrum disorders
ELBW—extremely low birth weight
MD—mean difference
OR—odds ratio
SGA—small for gestational age
VLBW—very low birth weight

Dr Pyhäälä participated in acquisition of the data, carried out the analyses and interpreted the data, drafted the initial manuscript, and critically revised the manuscript for important intellectual content; Drs Hovi, Kajantie, and Räikkönen conceptualized and designed the study, participated in acquisition of the data, interpreted the data, and critically revised the manuscript for important intellectual content; Drs Lahti, Heinonen, Pesonen, and Strang-Karlsson participated in acquisition of the data, carried out the analyses and interpreted the data, and critically revised the manuscript for important intellectual content; Ms Sammallahti carried out the analyses and interpreted the data and critically revised the manuscript for important intellectual content; Dr Eriksson conceptualized and designed the study and critically revised the manuscript for important intellectual content; Drs Andersson and Järvenpää conceptualized and designed the study, participated in acquisition of the data, and critically revised the manuscript for important intellectual content; and all authors approved the final manuscript as submitted.

WHAT’S KNOWN ON THIS SUBJECT: Preterm birth and faster infant growth have been identified as independent risk factors for autism-spectrum disorders (ASD). However, associations between prematurity and ASD-related traits as a continuum and effects of infant growth among those born preterm are still little studied.

WHAT THIS STUDY ADDS: VLBW young adults reported higher levels of ASD-related traits, particularly traits related to poorer social skills. Within the VLBW group, faster growth in weight, height, and head circumference from birth to term was associated with lower levels of ASD-related traits.

abstract

OBJECTIVES: We examined whether adults born preterm at very low birth weight (VLBW; <1500 g) differ from term-born adults in autism-spectrum traits, and whether among VLBW adults, growth in infancy is associated with these traits.

METHODS: A total of 110 VLBW and 104 term-born adults of the Helsinki Study of Very Low Birth Weight Adults completed the Autism-Spectrum Quotient yielding total, social interaction, and attention to detail sum scores. Growth in weight, length, and head circumference from birth to term and from term to 1 year of corrected age was determined as standardized residuals reflecting growth conditional on previous history.

RESULTS: VLBW adults scored higher than term-born controls on social interaction sum score, indicating higher autism-spectrum traits. In contrast, they scored lower on attention to detail sum score, indicating lower autism-spectrum traits. Within the VLBW group, faster growth in weight, length, and head circumference from birth to term was associated with lower total and social interaction sum scores. In this group, growth from term to 1 year was not associated with autism-spectrum traits.

CONCLUSIONS: Among those born preterm at VLBW, the risk for higher levels of autism-spectrum traits, particularly related to social interaction, may persist into adulthood. Faster growth from birth to term may ameliorate these effects, suggesting that targeted interventions could aid long-term neurodevelopment. Pediatrics 2014;134:1075–1083
Population-based studies show that young adults born preterm move from their parental home and start a family later than their peers born at term.\textsuperscript{1–3} Potentially related, preterm birth (<37 weeks of gestation) and low (<2000 g), very low (VLBW <1500 g), or extremely low (ELBW <1000 g) birth weight are associated with poorer social skills and higher rates of internalizing problems in childhood\textsuperscript{4,5} and adulthood.\textsuperscript{6–11} Furthermore, unimpaired children and adults born preterm score higher on attention problems\textsuperscript{4,12} and other symptoms of attention-deficit/hyperactivity disorder\textsuperscript{13} and lower on neurocognitive tests.\textsuperscript{14–17} This pattern of altered social, emotional, and cognitive development that characterizes individuals born preterm is reminiscent of that in autism-spectrum disorders (ASD).

Correspondingly, in large Scandinavian register studies, preterm birth has been associated with an increased risk for ASD diagnosis in children and adults.\textsuperscript{1,18,19} both with and without comorbid intellectual disability.\textsuperscript{20} Also in studies using diagnostic interviews for parents, children born preterm have been diagnosed with ASD more often than term-born peers.\textsuperscript{21,22}

However, cohort studies comparing those born preterm and term-born in subclinical ASD-related traits are still scarce. Autism-spectrum lies on a continuum of behavioral traits and symptoms where ASD represents 1 categorical end.\textsuperscript{23} In comparison with relatively rare categorical diagnoses, assessing ASD-related traits as dimensions offers more detailed information on these behaviors, not only among those who have ASD, but across the whole population. In the few existing studies, children born at <26 weeks of gestation were parent- and teacher-rated\textsuperscript{21} and VLBW adolescents were self- and parent-rated\textsuperscript{12,24} as having more ASD-related traits than term-born peers. It remains unknown if the effects of preterm birth on ASD-related traits persist into adulthood.

Several studies have shown that faster growth, particularly in length and head circumference, may be beneficial for neurodevelopment.\textsuperscript{25,26} By contrast, the existing data from studies focusing on infants born at term suggest that ASD is rather predicted by faster growth in head circumference,\textsuperscript{27} length, and weight\textsuperscript{28–30} during the first year of life. However, the 1 study that tested this association specifically in preterm children was not consistent with this.\textsuperscript{31}

The first objective of our study was to test the hypothesis that adults born preterm with VLBW report more ASD-related traits than their term-born counterparts. In line with previous literature on mental health,\textsuperscript{10,13} we also tested whether VLBW adults born small for gestational age (SGA) rather than appropriate for gestational age (AGA) report higher scores on ASD-related traits. The second objective was to test if growth in weight, length, or head circumference in infancy among those born preterm at VLBW is associated with ASD-related traits in young adulthood.

METHODS

Participants

The study was part of the second adult follow-up of the Helsinki Study of Very Low Birth Weight Adults. Details have been described elsewhere.\textsuperscript{10,16,32} The original cohort consisted of 335 infants born preterm at VLBW in 1978 to 1985 and discharged alive from hospital (survival rate, 70.7%). A control group (survival rate, 70.7%). A control group that included 314 individuals recruited from the same population was also included. Participants in the control group were matched for maternal age, sex, and control participants (Table 1). None reported an ASD diagnosis. In the perinatal and early health data, nonparticipation in the VLBW group was related to younger maternal age at delivery (28.7 vs 30.4 years; \(P = .005\)) and more frequent cerebral palsy diagnosis at age 15 months (15% vs 5%; \(P = .01\)).\textsuperscript{32} (\(P\) values were >0.14 for differences between nonparticipants and participants in the control group.)

The study protocol was approved by the Ethics Committee of the Helsinki University Central Hospital. All participants gave written informed consent.

Growth Data in the VLBW Group

Weight, length, and head circumference at birth came from hospital records (Table 1). Within the VLBW group, body size measures at term (40 weeks’ postmenstrual age) and 1 year of corrected age (92 weeks’ postmenstrual age) were interpolated using measurements from hospitals and child welfare clinics (Table 1). Body size at term was interpolated only if the time distance to the closest measurement point was ≤28 days. To minimize attrition, body size at 1 year of corrected age was interpolated if the time distance to the closest measurement point was ≤42 days.

To determine attained weight, length, and head circumference at birth and at term, and length and head circumference at 1 year of corrected age, the absolute measures of size were transformed into SD units according to Finnish growth standards in relation to gestational age in boys and girls separately.\textsuperscript{35–36} Weight at 1 year of corrected age is presented in Finnish growth standards as percent of the expected weight for gender and corrected age.\textsuperscript{34–36}
### Table 1: Descriptive Characteristics of the VLBW and Term-Born Control Groups

<table>
<thead>
<tr>
<th></th>
<th>VLBW</th>
<th>AGA (n = 69)</th>
<th>SGA (n = 41)</th>
<th>Control (n = 104)</th>
<th>Data missing, n (AGA/SGA/Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0/0/0</td>
</tr>
<tr>
<td>Perinatal data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>29.3 (2.4)a</td>
<td>28.0 (1.6)b</td>
<td>31.4 (1.8)b</td>
<td>40.1 (1.1)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>1131 (216)a</td>
<td>1126 (220)a</td>
<td>1139 (211)a</td>
<td>3613 (480)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Head circumference at birth, cm</td>
<td>26.3 (2.0)a</td>
<td>25.8 (2.0)b</td>
<td>27.1 (1.8)b</td>
<td>35.0 (1.2)</td>
<td>3/0/0</td>
</tr>
<tr>
<td>Birth weight for gestational age, SD units</td>
<td>1.29 (1.55)a</td>
<td>0.27 (0.85)b</td>
<td>-3.01 (0.70)b</td>
<td>0.08 (1.06)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Head circumference for gestational age at birth, SD units</td>
<td>2.01 (0.70)a</td>
<td>2.08 (1.02)b</td>
<td>0.10 (1.06)</td>
<td>504 (1.3)</td>
<td>2/0/0</td>
</tr>
<tr>
<td><strong>Maternal age at birth, y</strong></td>
<td>30.4 (5.6)</td>
<td>29.7 (4.3)</td>
<td>31.5 (5.0)</td>
<td>29.6 (5.2)</td>
<td>0/0/0</td>
</tr>
<tr>
<td><strong>Paternal age at birth, y</strong></td>
<td>32.0 (5.6)</td>
<td>31.6 (5.0)</td>
<td>32.6 (6.5)</td>
<td>31.8 (6.0)</td>
<td>0/0/0</td>
</tr>
<tr>
<td><strong>Pre-eclampsia, n (%)</strong></td>
<td>27 (26.0)d</td>
<td>7 (10.9)b</td>
<td>20 (50.0)a,b</td>
<td>9 (9.0)</td>
<td>5/1/4</td>
</tr>
<tr>
<td>Maternal smoking during pregnancy, n (%)</td>
<td>19 (18.6)</td>
<td>12 (19.4)</td>
<td>7 (17.5)</td>
<td>16 (15.8)</td>
<td>7/1/5</td>
</tr>
<tr>
<td><strong>Multiple birth, n (%)</strong></td>
<td>18 (16.4)a</td>
<td>10 (14.5)a</td>
<td>8 (19.5)a</td>
<td>0 (0.0)</td>
<td>2/0/0</td>
</tr>
<tr>
<td><strong>Duration of ventilator treatment, median days (25th/75th percentiles)</strong></td>
<td>4 (0/14)</td>
<td>6 (0/28)</td>
<td>1 (0/10)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of supplemental oxygen, median days (25th/75th percentiles)</strong></td>
<td>10 (2/35)</td>
<td>17 (5/43)</td>
<td>5 (1/18)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>Septicemia, n (%)</strong></td>
<td>10 (9.3)</td>
<td>5 (7.5)</td>
<td>5 (12.5)</td>
<td>N/A</td>
<td>2/1/0</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>None, n (%)</strong></td>
<td>70 (84.3)</td>
<td>40 (80.0)</td>
<td>30 (90.9)</td>
<td>N/A</td>
<td>19/8/ N/A</td>
</tr>
<tr>
<td>Grade I or II, n (%)</td>
<td>9 (10.8)</td>
<td>7 (14.0)</td>
<td>2 (6.1)</td>
<td>N/A</td>
<td>5/1/0</td>
</tr>
<tr>
<td>Grade III or IV, n (%)</td>
<td>4 (4.8)</td>
<td>3 (6.0)</td>
<td>1 (3.0)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia, n (%)</td>
<td>25 (23.6)</td>
<td>19 (28.4)</td>
<td>6 (15.4)</td>
<td>N/A</td>
<td>2/2/ N/A</td>
</tr>
<tr>
<td>Received indomethacin, n (%)</td>
<td>35 (32.4)</td>
<td>27 (39.9)</td>
<td>8 (20.0)</td>
<td>N/A</td>
<td>1/1/ N/A</td>
</tr>
<tr>
<td>Surgery owing to patent ductus arteriosus, n (%)</td>
<td>8 (7.4)</td>
<td>7 (10.3)</td>
<td>1 (2.5)</td>
<td>N/A</td>
<td>1/1/ N/A</td>
</tr>
<tr>
<td>Blood exchange transfusion owing to hyperbilirubinemia, n (%)</td>
<td>15 (14)</td>
<td>11 (16.4)</td>
<td>4 (10)</td>
<td>N/A</td>
<td>2/1/ N/A</td>
</tr>
<tr>
<td>Age at discharge from birth hospital, median days (25th/75th percentile)</td>
<td>70 (51/90)</td>
<td>72 (53/90)</td>
<td>85 (45/84)</td>
<td>N/A</td>
<td>31/21/ N/A</td>
</tr>
<tr>
<td>Size in infancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight at term, g</td>
<td>2508 (526)</td>
<td>2678 (480)</td>
<td>2221 (480)</td>
<td>N/A</td>
<td>2/1/ N/A</td>
</tr>
<tr>
<td>Weight at 1 y of corrected age, g</td>
<td>8573 (1124)</td>
<td>8727 (1078)</td>
<td>8303 (1170)</td>
<td>N/A</td>
<td>15/8/ N/A</td>
</tr>
<tr>
<td>Length at term, cm</td>
<td>46.0 (2.7)</td>
<td>48.6 (2.5)</td>
<td>44.6 (2.4)</td>
<td>N/A</td>
<td>4/2/ N/A</td>
</tr>
<tr>
<td>Length at 1 y of corrected age, cm</td>
<td>73.1 (2.8)</td>
<td>73.4 (2.8)</td>
<td>72.7 (2.8)</td>
<td>N/A</td>
<td>14/11/ N/A</td>
</tr>
<tr>
<td>Head circumference at term, cm</td>
<td>33.7 (2.0)</td>
<td>34.1 (2.0)</td>
<td>33.0 (1.8)</td>
<td>N/A</td>
<td>5/4/ N/A</td>
</tr>
<tr>
<td>Head circumference at 1 y of corrected age, cm</td>
<td>45.6 (1.4)</td>
<td>45.7 (1.5)</td>
<td>45.4 (1.4)</td>
<td>N/A</td>
<td>28/17/ N/A</td>
</tr>
<tr>
<td>Adulthood data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest education of either parent, n (%)</td>
<td>10 (9.1)</td>
<td>6 (8.7)</td>
<td>4 (8.8)</td>
<td>6 (5.8)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Elementary</td>
<td>10 (9.1)</td>
<td>6 (8.7)</td>
<td>4 (8.8)</td>
<td>6 (5.8)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>High school</td>
<td>22 (20.0)</td>
<td>9 (13.0)</td>
<td>13 (17.3)</td>
<td>N/A</td>
<td>1/1/0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>44 (40.0)</td>
<td>32 (46.4)</td>
<td>12 (19.3)</td>
<td>N/A</td>
<td>19/1/ N/A</td>
</tr>
<tr>
<td>University</td>
<td>34 (30.8)</td>
<td>22 (31.9)</td>
<td>12 (19.3)</td>
<td>48 (44.2)</td>
<td>34/17/ N/A</td>
</tr>
<tr>
<td>Age at assessment, y</td>
<td>250.0 (21.2)</td>
<td>252.2 (22.2)</td>
<td>247.9 (19.9)</td>
<td>251.2 (22.2)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Attention-deficit/ hyperactivity problems, n (%)</td>
<td>12 (11.4)</td>
<td>7 (10.8)</td>
<td>5 (12.5)</td>
<td>11 (10.5)</td>
<td>4/1/0</td>
</tr>
<tr>
<td>Anxiety problems, n (%)</td>
<td>5 (4.8)</td>
<td>3 (4.8)</td>
<td>2 (5.0)</td>
<td>7 (6.7)</td>
<td>4/1/0</td>
</tr>
<tr>
<td>Neurosensory impairments, n (%)</td>
<td>9 (8.2)c</td>
<td>5 (7.2)c</td>
<td>4 (8.8)c</td>
<td>1 (1.0)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Severe hearing impairment</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.0)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Blindness</td>
<td>2 (1.8)</td>
<td>1 (1.4)</td>
<td>1 (2.4)</td>
<td>0 (0.0)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>6 (5.5)</td>
<td>4 (5.8)</td>
<td>2 (4.9)</td>
<td>0 (0.0)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Developmental disability</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>1 (2.4)</td>
<td>0 (0.0)</td>
<td>0/0/0</td>
</tr>
</tbody>
</table>

Mean (SD) is given unless otherwise indicated.

a P < .001 against the term-born control group.
b P < .001 between the VLBW-AGA and VLBW-SGA groups.
c P < .05 against the term-born control group.
d P < .01 against the term-born control group.
e P < .05 between the VLBW-AGA and VLBW-SGA groups.
f Number of individuals scoring at or above the cutoff indicative of problems of borderline clinical significance.
To facilitate intrapersonal comparisons, we gender-standardized the percent values within the VLBW group.

The postnatal conditional growth variables were gender-standardized residuals from linear regression models in which the attained body size measure (weight, length, and head circumference) at term was regressed on the corresponding measure at birth, and the attained body size measure at 1 year of corrected age was regressed on the corresponding measure at term. The obtained growth variables are uncorrelated residuals and can be interpreted as growth since previous measurement.37

**Autism-Spectrum Traits**

The Autism-Spectrum Quotient (AQ)38 comprises 50 items self-rated on a 4-point scale. Responses were dichotomized: “definitely agree” and “slightly agree” were assigned 1 and “slightly disagree” and “definitely disagree” 0 in half of the items, whereas in the other half the scoring was opposite. A higher total sum score (range, 0 to 50) indicates higher and/or stronger ASD-related traits; scores ≥20 indicate at least intermediate levels.38 The AQ also yields a social interaction sum score, which combines 40 items relating to social and communication skills, imagination, and attention switching abilities, and an attention to detail sum score combining 10 items.39 The AQ scale has been shown to have good discriminant validity.38 In our sample, internal consistency (Cronbach’s α) for the total, social interaction, and attention to detail sum scores were 0.78, 0.81, and 0.57, respectively.

**Covariates and Confounders**

Date of birth, gestational age at birth, multiple birth, mother’s age at delivery, maternal pre-eclampsia, maternal smoking during pregnancy, and neonatal treatments and complications came from hospital records. Dated measurements of body size between birth and 1 year of corrected age were collected from the hospital records and child welfare clinics. Elapsed time in days between the closest measurement and the age of interest was calculated. Diagnosed neurosensory impairments (cerebral palsy, developmental disability, blindness, and hearing impairment) and parents’ education (highest of either parent) were self-reported on the first clinical visit in adulthood. Attention-deficit/hyperactivity problems and anxiety problems were self-rated using the Adult Self-Report (we used the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition oriented scales and cutoffs to identify individuals who had problems of borderline clinical significance) in conjunction with the AQ.40

**Statistical Analyses**

Square root transformations of the skewed total and social interaction sum scores were computed to attain normality. All AQ scores were then standardized to facilitate interpretation.

**Comparisons Between the VLBW and Term-Born Groups**

Descriptive characteristics were compared between the VLBW and term-born groups with Student’s t test or Pearson’s χ² test. We used linear regression analyses to examine group differences in AQ scores, and logistic regressions for scoring ≥20 points (intermediate cutoff) on the total sum score. We then examined the same outcomes by contrasting VLBW-AGA and VLBW-SGA groups against the term-born controls and each other.

We made adjustments for gender and age (model 1) and further for mother’s age at delivery, maternal pre-eclampsia, smoking during pregnancy, and parental education (model 2). In model 3, we further adjusted for attention-deficit/hyperactivity and anxiety problems and excluded those who had neurosensory impairments.

**RESULTS**

**Comparisons Between the VLBW and Term-Born Groups**

In comparison with adults who were term-born, VLBW adults scored higher (indicating higher ASD-related traits) on the social interaction sum score.
and social interaction sum scores (models 1–3) and lower on the attention to detail sum score (models 1–3) (Table 2).

The VLBW-AGA and VLBW-SGA groups did not differ from each other on AQ scales ($P$ values $\geq 0.44$). In comparison with adults who were term-born, the VLBW-AGA group scored lower on the attention to detail sum score (mean difference [MD], $-0.28$ SD units; 95% confidence interval [CI], $-0.60$ to 0.03; $P = .07$ in model 1, $P = .06$ in model 2, and $P = .04$ in model 3). The VLBW-SGA group scored higher on the social interaction sum score (MD, 0.5; 95% CI, 0.12 to 0.78; $P = .01$ in model 1, $P = .02$ in model 2, and $P = .06$ in model 3) and lower on the attention to detail sum score (MD, $-0.37$; 95% CI, $-0.70$ to $-0.03$; $P = .03$ in model 1, $P = .23$ in model 2, and $P = .28$ in model 3) and more often above the intermediate cutoff on the total sum score (OR, 2.28; 95% CI, 1.01 to 5.17; $P = .048$ in model 1, $P = .05$ in model 2, and $P = .06$ in model 3) than controls.

**Growth in Infancy in the VLBW Group**

Figure 1 and Supplemental Table 1 (available online) show that VLBW adults who grew faster in weight from birth to term scored lower on the total and social interaction sum scores (models 1–3) and had lower odds of scoring above the intermediate cutoff on the total sum score (model 1). Faster growth in length during this period predicted lower total score (model 1). Those who were heavier at term scored lower on the total and social interaction sum scores (models 1 and 2). Those who were longer at term scored lower on total and social interaction sum scores (model 1). Those who had larger head circumference at term scored lower on the total and social interaction sum scores (model 1), and had a lower odds of scoring above the intermediate cutoff on total sum score (model 1). Those who were heavier and longer at 1 year of corrected age had a lower odds of scoring above the intermediate cutoff on total sum score (models 1–3), and those who had a larger head circumference at 1 year of corrected age scored lower on the total and social interaction sum scores (model 1).

**Discussion**

In comparison with term-born controls, VLBW young adults reported approximately 0.2 to 0.4 SD units higher levels of ASD-related traits, particularly traits related to poorer social and communication skills and preferences. This corresponds to our hypothesis and previous register

| Table 2 Mean Scores (SD) for AQ Scales in the VLBW and Term-Born Control Groups, and Mean Differences Between the Groups in SD Units, and OR for Having the Total Sum Score at or Above the Intermediate Cutoff of 20 |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| VLBW ($n = 110$) | Control ($n = 104$) | VLBW versus Control Mean difference/OR (95% CI) |
| Mean (SD) | Mean (SD) | Model 1 | Model 2 | Model 3 |
| Total sum score | 16.44 (6.68) | 15.04 (5.88) | 0.20 ($−0.07$ to 0.47) | 0.23 ($−0.05$ to 0.52) | 0.19 ($−0.10$ to 0.48) |
| Social interaction sum score | 12.48 (6.33) | 10.38 (5.33) | 0.32 ($0.06$ to $0.59$) | 0.34 ($0.06$ to $0.63$) | 0.31 ($0.02$ to $0.59$) |
| Attention to detail sum score | 3.95 (2.13) | 4.04 (2.05) | $−0.32$ ($−0.59$ to $−0.06$) | $−0.30$ ($−0.58$ to $−0.01$) | $−0.32$ ($−0.62$ to $−0.03$) |

Model 1 refers to adjustments made for gender and age, model 2 further for parental education, mother’s age at participant’s birth, maternal pre-eclampsia, and maternal smoking during pregnancy, and model 3 after excluding the 10 participants who had neurosensory impairments and adjusting further for attention-deficit/hyperactivity and anxiety problems.

* None of the individuals available for this analysis scored above the cutoff indicative of borderline clinically significant attention-deficit/hyperactivity or anxiety problems.

* $P < .05$
AQ total and social interaction sum scores. This suggests that faster growth in early infancy may benefit VLBW adults across the entire range of ASD-related symptoms and behaviors, but those related to social skills and preferences in particular. However, we found no consistent associations between growth between term and 1 year of corrected age and ASD-related traits. VLBW-SGA/VLBW-AGA status did not modify the effects of growth on ASD-related traits notably. Our findings add to the literature by showing that the increased risk for ASD symptoms and traits after preterm birth persists into young adulthood. We also demonstrated that preterm birth at VLBW may not pose a risk for the entire range of ASD-related traits, but the risks are specific to characteristics of social interaction. Our finding is in line with previous results of increased shyness and social problems or less sociability among preterm young adults. 

**FIGURE 1**

Associations between growth in infancy and AQ scales in VLBW adults. A, Associations between growth from birth to term and AQ scores. B, Associations between growth from term to 1 year of corrected age and AQ scores. Error bars show the increase and its 95% CI in SD units on an AQ scale per 1 SD unit faster growth in weight, length, and head circumference.

**FIGURE 2**

Associations between attained body size SD scores at birth, term, and 1 year of corrected age and AQ scales in VLBW adults. Error bars show the difference and its 95% CI in SD units on an AQ scale per 1 SD unit higher weight, length, and head circumference. Weight at 1 year of corrected age is determined as an SD score according to the VLBW sample. Other size measures are SD scores according to Finnish growth curves. Analyses are adjusted for gender, gestational age at birth, age at testing, parental education, mother’s age at participant’s birth, maternal pre-eclampsia, and maternal smoking during pregnancy (model 1). Analyses using body size at term or at 1 year of corrected age are also adjusted for the time distance between the interpolated value and the nearest actual value.
autism-spectrum behavior. As a novel finding, our findings suggest that the effects of preterm birth on ASD-related traits were independent of comorbid attention-deficit/hyperactivity and anxiety problems, highlighting the specificity of the association between preterm birth and ASD.

We and others have previously reported that preterm children, adolescents, and young adults show more neurocognitive and executive problems, including inattentiveness. Hence, the lesser attention to detail found in the current study may reflect cognitive challenges related to inattentiveness rather than characteristic traits related to ASD. Yet our findings relating to attention to detail must be interpreted with caution, as the internal consistency of this scale was relatively low. Low internal consistency of this scale has also been reported by others. As previously suggested, these cognitive challenges may also contribute to the difficulties in social relations of the VLBW adults. Such challenges may hamper detection of more subtle details in social interaction. Consequently, the higher rate of neurocognitive, executive, and social difficulties may all be interrelated and manifest in behaviors resembling ASD. Our results of poorer social skills and attention to detail in VLBW adults lend support to the idea of a “preterm behavioral phenotype” including inattention, internalizing behavior, and social difficulties.

In our study, faster growth in weight, length, and head circumference between birth and term predicted lower ASD-related traits. This association was partially independent of major neonatal complications, suggesting that more subtle variation in prerequisites of growth, including nutrition, may be an underlying factor. Previously, it has been shown that among children born preterm, smaller head circumference for length at 1 year of corrected age was associated with an ASD diagnosis. In contrast, studies not focusing on individuals born preterm show harmful effects of faster infant growth, including increased risk for an ASD diagnosis. The discrepancy implies that the underlying mechanisms of ASD and ASD-related traits may depend on prematurity.

Our results gain support from studies showing that faster infant growth predicts better neurocognitive performance. Subtle perinatal neural insults and subsequent alterations in brain development during the neonatal period have been suggested as an underlying mechanism for later neurocognitive and social behavioral problems in infants born preterm, also in those who do not have severe neurosensory injury. Thus, in addition to potential pregnancy complications and altered intrauterine growth environment, the early postnatal environment affecting the growth immediately after preterm birth may be of major importance for neurodevelopment.

A study limitation is that we cannot make causal inferences or specify underlying mechanisms. Furthermore, self-reported ASD-related traits were not confirmed by direct observation or parent or partner reports. The absence of self-reported ASD diagnoses may reflect attrition in this intensive follow-up study, but it may also reflect that in the childhood of this cohort the diagnostic awareness of ASD was lower than today. However, our focus was on ASD-related traits, not on diagnostic entities, and when comparing those with and without available growth data, we found very little difference in ASD-related traits, suggesting that attrition is unlikely to have caused severe bias. Study strengths include extensive perinatal and infant growth data, data on various behavioral phenotypes, and the longitudinal study design. This enabled us to examine the associations between early postnatal growth and ASD-related traits in adulthood, whereas earlier research on growth and ASD has been conducted almost exclusively among children. This also enabled us to make adjustments for psychiatric symptomatology that often accompanies ASD-related traits, namely attention-deficit/hyperactivity and anxiety problems.

Among individuals born preterm, the risk for higher levels of autism-spectrum traits, particularly those related to skills and preferences in social interaction, may persist into young adulthood. This is the first study to show that faster growth after preterm birth may ameliorate these effects, suggesting a window of opportunity for targeted interventions to benefit long-term neurodevelopment.

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