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Running title: Early-life exposures and cognitive development

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Manuscript title (please type): Associations of early-life exposures and socioeconomic status with cognitive development at school-age

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All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication.

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Associations of Early-Life Exposures and Socioeconomic Status with Cognitive Development at Preadolescence

Running title: Early-life exposures and cognitive development

Wasef Na’amnih, PhD¹, Ashraf Akawi, MA², Ahmad Abu-Moch, MA², Rinat Cohen, MA³, Gal Dror, MD¹, Eias Kassem, MD⁴, Khitam Muhsen*, PhD¹⁸, Asher Ornoy*, MD⁵

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Associations of early-life exposures and socioeconomic status with cognitive development at preadolescence

Running title: Early-life exposures and cognitive development
Abstract

**Background:** The long-term relations of socioeconomic status (SES) and early-life exposures with cognitive development at preadolescence are not fully understood, especially in low SES populations. We examined associations of SES and early-life exposures including feeding practices, physical growth and infections with cognitive development among preadolescents from underprivileged communities.

**Methods:** A prospective study was conducted among 146 healthy children from two relatively low SES Arab villages in Israel, who were recruited at age 1–9 weeks and followed until age 18 months. Information was obtained on their feeding practices, health status and growth indicators. Cognitive development at age 10–12 years was assessed using the Wechsler Intelligence Scale, including the full-scale intelligence quotient (FSIQ) and scores of four cognitive domains. Multiple linear regression models were performed.

**Results:** Nearly all the children (98%) were breastfed in infancy. Bivariate correlations were found of SES, growth indices and rates of diarrheal and respiratory illnesses in infancy, but not of feeding practices, with cognitive scores. In multivariable models, SES was positively (p <0.001) associated with all the cognitive domains (beta coefficient ranges 4.3 to 8.2). Birthweight was positively associated with FSIQ (p = 0.039) and the perceptual reasoning index (p = 0.002). Weight for age Z score at age 10–14 months was positively associated with the verbal comprehension index (p = 0.003). The rate of respiratory illnesses was negatively associated with the perceptual reasoning index (p = 0.05).

**Conclusions:** SES is strongly associated with cognitive development even in relatively low SES communities. Birthweight, weight indicators and respiratory illness in infancy might affect cognitive development through preadolescence.

**Key Words:** birthweight; cognitive development; preadolescence; socioeconomic status
Introduction

Cognitive performance and skills during childhood have long-term impact on academic attainment at school-age and in adulthood.\(^1,2\) Moreover, lower cognitive scores during childhood and adolescence might increase risk of cardiovascular and metabolic diseases in adulthood.\(^3\) Parental education and socioeconomic status (SES) are important determinants of children’s cognitive development, together with genetics, nutrition, iron deficiency anemia, the parent-child interaction and chronic diseases.\(^4-13\) Children from disadvantaged backgrounds and those with low parental education display inferior cognitive achievements compared to children from affluent families.\(^9,14-18\) Importantly, the negative impact of SES on cognitive abilities may be mitigated through child enrichment activities.\(^9,15\) Thus, identifying children at risk of diminished cognitive abilities in economically disadvantaged populations enables implementation of programs that may improve long-term educational outcomes.

Neonatal risks such as prematurity and low birthweight,\(^18,19\) and post-natal risks such as poor physical growth\(^20\) and health status (e.g., hospitalizations\(^21\) and gastrointestinal infections\(^17,20\)) may influence cognitive abilities, school readiness skills\(^21\) and performance.\(^22,23\) Moreover, breastfeeding and feeding practices in infancy were shown to affect children’s cognitive development throughout childhood.\(^4,5,24\) Some of these factors, such as breastfeeding and gastrointestinal infections, are affected by SES and culture. Therefore, it is important to assess the impact of neonatal and postnatal risks on children’s cognitive development in social- and culture-specific contexts.

Gaps of knowledge remain regarding the determinants of cognitive development in children, particularly with regard to the long-term relations of early-life exposures and SES with cognitive development at school age in underprivileged communities. Moreover, most
prior studies focused on toddlers, preschoolers and children at early school age, while preadolescents have been less frequently studied. Preadolescence usually refers to ages 10–13 years, during which early biological events of puberty, neurological changes and psychological tasks of adolescence are initiated. Preadolescence is suggested as a distinct period, characterized by premonitory bodily changes, an internal sense of imbalance and amplified conflict in the parent-child relationship. Thus, understanding the role of early-life exposures on cognitive abilities during the sensitive developmental period of preadolescence is essential. Accordingly, the current study examined associations of early-life exposures including feeding practices, physical growth and morbidity with cognitive development at preadolescence. Our hypothesis was that, beyond SES, early-life exposures might have a persistent influence on cognitive development at preadolescence.
Methods

Study design and population

A cohort study was conducted among 233 children from two neighboring Arab villages located in the Hadera sub-district, herein referred to as village A and B. According to the Central Bureau of Statistics, these villages are categorized as cluster 2 SES, on a scale of 1–10, with 10 being the highest socioeconomic rank (wealthiest). Overall, 18.7% and 35.8% of the families in villages A and B, respectively, have ≥4 children, compared to 18.0% of the general population. The mean respective schooling years of adults aged 25–54 years are 10.2 and 8.4 years, compared to 12.2 years nationwide. The respective percentages of workers receiving below minimum wage are 51.0% and 53.7%, compared to 42.3% nationwide.

Children born in 2006–2007 were recruited at age 1–9 weeks during the period of January–August 2007, through the maternal and child health clinics in the villages. Inclusion criteria were: 1) birthweight >2 kilogram; 2) gestational age at birth >34 weeks; 3) singleton birth; 4) no prenatal/perinatal complications (e.g., perinatal asphyxia); and 5) no diagnosis of major birth defects (e.g., major heart malformations, hydrocephalus), chronic diseases (e.g., renal failure) or genetic disorders that might affect growth and development. From the follow-up study, we excluded children with developmental delays who had educational special needs.

This follow-up at preadolescence (10–12 years) was undertaken during the period 2017–2019. Of the 207 (88.8%) families we located, 174 (84.1%) agreed to participate and 146 (83.9%) children completed the cognitive assessment (Figure 1).

Data collection
Data on early-life exposures were collected during the period 2007–2009 through maternal interviews (in Arabic) at enrollment, follow-up interviews/visits and medical records. Information on pre- and perinatal history was validated against medical records. At age 10–12 years, parents were interviewed (face-to-face) in Arabic to collect updated socioeconomic data and children’s health status using structured questionnaires. The interviewers received standardized training.

**The dependent variable – cognitive development**

Cognitive development at age 10–12 years was assessed by two trained Arabic-speaking psychologists (AA and AAM) using the Arabic version of the Wechsler Intelligence Scale for Children, fourth edition (WISC®-IV). This validated test yields an overall full-scale intelligence quotient (FSIQ) score, and scores of four cognitive domains: verbal comprehension index (VCI), working memory index (WMI), processing speed index (PSI) and perceptual reasoning index (PRI). Cognitive scores were analyzed as continuous variables. The two examiners were blinded to the participants’ background characteristics. Children underwent the evaluations in a relaxed and quiet environment with adequate lighting, under similar conditions.

**The independent variables**

The independent variables were selected based on previous evidence of possible associations with aspects of children’s cognitive development.

Sociodemographic data: Information was obtained on children’s age at the current examination (continuous variable), sex, residential village, and maternal and paternal schooling years. The number of schooling years corresponded well with the highest
educational level that the parents achieved. We considered in the analysis the number of schooling years rather than the educational level, as the data were more complete for that variable. Household density was calculated as the number of persons living in a household divided by the number of rooms. A SES composite index was calculated using a factor analysis and included the following variables: residential village, the number of maternal and paternal schooling years (assessed as the last year of school) and household density at the follow-up examination. Higher values of the composite SES index represent better SES.

Feeding practices in early life: Information was obtained via maternal reports in interviews conducted at enrollment and at ages 2, 4, 6, 8, 12 and 18 months using a structured questionnaire. Information was collected on infants’ feeding habits: breastfeeding (yes or no); duration of breastfeeding (in months); and the respective ages that formula, solid foods and herbal tea were introduced. Although not included in nutritional guidelines in infancy, herbal tea was commonly given in infancy to the study population. A lower age of introducing herbal tea was shown to be associated with an increased likelihood of early breastfeed weaning in this population.28

Growth indices: Information on height and weight measurements at ages 10–14 months were retrospectively obtained from medical records at maternal and child health clinics. Weight for age Z (WAZ), weight for height Z (WHZ) and height for age Z (HAZ) scores were calculated using the World Health Organization (WHO) reference population for children aged 0–59 months.32

Hemoglobin (mg/dL) level (a continuous variable): Anemia is screened in Israel at age 9–18 months. Data on hemoglobin were retrospectively collected from medical records.
Gestational age at birth (in weeks) and birthweight (in grams) were defined based on data from medical records at recruitment and analyzed as continuous variables.

Diarrheal diseases: Information was obtained via fortnightly active surveillance at ages 2–18 months. Diarrhea was defined as three or more watery stools during a 24-hour period. The diarrheal disease rate was calculated as the number of episodes divided by the follow-up time.

Respiratory illnesses: Information was obtained via fortnightly active surveillance at ages 2–18 months. The respiratory illnesses rate was calculated as the number of episodes divided by the follow-up time.

**Data management**

Data obtained through interviews and measurements were subjected to quality control checks to assess completeness and consistency, and analyzed using IBM SPSS version 27 (Armonk, NY: IBM Corp) and Winpepi. WHO Anthro software was used to calculate HAZ, WHZ and WAZ scores, compared to the WHO growth charts using information on anthropometric measurements, date of measurements, and children’s birth date and sex.

**Statistical methods**

Baseline sociodemographic and early-life exposures were compared between participants of this follow-up study and the entire cohort using descriptive statistics (means and standard deviations [SD] for continuous variables, medians and interquartile ranges [IQR] for discrete variables, and counts and percentages for categorical variables). Differences in mean IQ scores according to categorical variables were examined using the Student’s t test. The Spearman’s rank correlation coefficient was used to examine correlations between cognitive
scores and independent continuous variables (e.g., SES score, birthweight, and growth indices). Multiple comparisons were corrected using the Benjamini-Hochberg false discovery rate method. Logarithmic transformation was performed for independent variables with skewed distribution. Multiple linear regression models were constructed separately for each cognitive domain. Birthweight and the SES composite score were included in all the models as independent variables; other variables were added to the models if they were associated with the cognitive score in a bivariate analysis with p < 0.1. Multicollinearity was assessed using the variance inflation factor, with no evidence of multicollinearity. The final model was selected based on model fit parameters. We also explored, in a mediation analysis using PROCESS macro for SPSS by Hayes 2018, whether the SES-IQ association might be explained by indirect effects via WAZ, respiratory illness or diarrheal diseases in infancy.

**Ethical aspects**

The study was conducted in accordance with the Declaration of Helsinki; all the procedures were performed in accordance with local guidelines and regulations. Protocols of both the 2007–2009 baseline (infancy) and 2017–2019 (preadolescence) studies were approved by the Ethics Committee of Tel Aviv University and the Institutional Review Board of Hillel Yaffe Medical Center (Protocol number 0030-16-HYMC). The children’s parents signed written informed consent.
Results

Description of the study sample

Overall, 146 children (58.2% boys) underwent the cognitive assessment at age 10–12 years; the mean age was 11.3 years (SD = 0.5). Sociodemographics, feeding practices, birthweight, gestational age at birth and growth indices were similar between the participants and the original infancy cohort (Table 1 and Supplementary Figure 1). Fifty-four (37.0%) lived in village A (the higher SES village) and 92 (63.0%) in village B (the lower SES village). During infancy, most participants were breastfed (98.6%), yet only 17.9% were exclusively breastfed. The mean duration of breastfeeding was 6.7 months (SD = 5.3). Formula and solid foods were introduced at mean ages of 1.9 months (SD = 1.3) and 5.0 months (SD = 1.2), respectively (Table 1).

Early-life exposures and cognitive scores at preadolescence

Mean cognitive scores did not differ significantly between boys and girls, except for a higher PSI score in girls (Supplementary Figure 2).

Significant positive correlations were found between the SES composite index and all the cognitive scores (Spearman’s correlation coefficient range 0.33 to 0.52). Gestational age at birth was positively correlated with the VCI score. Positive correlations were found of the HAZ score with FSIQ, VCI and PRI scores; and of the WAZ score with FSIQ, VCI and PSI scores, (The range of the Spearman’s correlation coefficient was 0.20 to 0.29). Negative correlations were found of diarrheal diseases with all the cognitive scores. Similar negative correlations were found between respiratory illnesses and the cognitive scores, except the PSI score. The age of introduction of herbal tea correlated negatively with most cognitive scores (The
range of the Spearman’s correlation coefficient was -0.21 to -0.36). These correlations remained significant (p < 0.05) after adjustment for multiple comparisons. No significant correlations were found of breastfeeding duration, age of introducing formula, WHZ, hemoglobin level and birthweight with the cognitive scores (Figure 2). Eleven mothers had gestational diabetes mellitus; no significant differences were observed in the FSIQ score (P = 0.57) or in any of the cognitive scores between offspring of mothers with gestational diabetes and offspring of mothers without gestational diabetes (P = 0.70, 0.78, 0.16 and 0.20 for the VCI, PRI, WMI and PSI scores, respectively).

**Multivariable analysis**

HAZ and WAZ scores were highly correlated (Spearman’s correlation coefficient 0.69, p < 0.001) and therefore assessed in separate models. A moderate correlation was found between respiratory and diarrheal disease rates in infancy (Spearman’s correlation coefficient 0.39, p < 0.001). Therefore, these variables were analyzed in separate models. Multivariable linear regression models showed strong positive correlations of the SES composite index with all the cognitive domains (p < 0.001). Birthweight was positively correlated with FSIQ (p = 0.039) and PRI scores (p = 0.002); similar trends, though not statistically significant, were found with VCI (p = 0.057) and PSI scores (p = 0.073). The WAZ score at age 10–14 months was positively associated with the VCI score (p = 0.003); a similar non-significant trend was found for the FSIQ score (p = 0.089). The rate of respiratory illnesses in infancy was negatively associated with the PRI score (p = 0.05). The mean PSI score was significantly higher among girls than boys (p = 0.001) (Table 2). Replacing the WAZ score with the HAZ score in these models showed no significant associations between HAZ
and cognitive scores (Supplementary Table 1). Adding gestational diabetes to the multivariable model did not change the results (Supplementary Table 2).

In multivariable models, significant correlations were not found between diarrheal disease and any of the cognitive domains (Supplementary Table 3).

**Mediation analysis**

The SES composite score was significantly negatively correlated with rates of diarrheal disease and respiratory illness in infancy (Spearman’s correlation coefficient -0.48 and -0.33). A positive correlation was found between diarrheal disease and the rate of respiratory illness in infancy (Spearman’s correlation coefficient 0.33); these were negatively correlated with the HAZ score in infancy (Spearman’s correlation coefficient -0.20 and -0.21) (Figure 3). In a mediation analysis that included respiratory illness and WAZ in infancy, and that adjusted for birthweight, the effect of the SES index on the FSIQ score was totally a direct effect (beta coefficient 8.2 [95% CI 5.8, 10.7]). No significant evidence was noted of indirect effects via respiratory illnesses (indirect effect size 0.5 [95% bootstrap CI -0.2, 1.5]) or WAZ in infancy (indirect effect size 0.07 [95% bootstrap CI -0.2, 1.3]). The results were similar when the variable respiratory illness was replaced by diarrheal disease in the model.
Discussion

We examined the long-term relations and the inter-relations of an SES composite index and early-life exposures, including in the neonatal and infancy periods, with cognitive development at preadolescence. The SES index was strongly correlated with overall cognitive development and with the four specific cognitive domains examined. While SES indicators were previously reported as determinants of children’s cognitive development,\(^9\)\(^{,}\)\(^{14}\)\(^{,}\)\(^{17}\) the strength of association in this study was remarkable. The SES index was correlated to children’s growth indicators and to rates of diarrheal and respiratory illness in infancy. However, these factors were not mediators in the association between SES and cognitive scores. SES is related to material deprivation (such as cognitive stimulation, nutrient deficiencies) and to stressors (e.g., negative parenting behaviors), and these might contribute to the SES-cognitive development association.\(^37\)\(^{,}\)\(^{38}\) The environment of poverty has been suggested as influencing neurodevelopment by depriving the brain of key stimuli and increasing its exposure to negative input.\(^38\) Indeed, the home learning environment\(^39\)\(^{,}\)\(^{40}\) and psychosocial aspects of caregiving, such as learning and language stimulation, and warmth and acceptance,\(^41\) were shown to be related to children’s cognitive development. Collectively, the findings highlight the need to reduce social disparities, and to target the poorest communities to close gaps in child cognitive development, academic achievements and health inequalities. A comprehensive multifaceted approach is required to reduce social health and educational inequalities. Interventions to reduce socioeconomic health differences, especially in maternal and child health, include improving access to care (financial and cultural), increasing immunization coverage, nutrition supplementation programs and health education, alongside personal support.\(^42\)\(^{,}\)\(^{43}\) Interventions that have
demonstrated effectiveness in improving educational achievements of elementary and middle school students from low SES include tutoring, providing feedback and monitoring progress, and cooperative learning. Closing social gaps targets the source of gaps in academic achievements. Interventions have been developed that provide individuals the skills and abilities necessary for academic achievement. Such interventions usually target children in elementary school or even pre-school, as the early years are critical for the acquisition of these skills. Additionally, structural interventions have been developed based on the premise that providing students from low SES the necessary material resources and opportunities (e.g., information and financial support) will reduce these gaps. Effective structural interventions usually focus on individuals who already possess the qualities needed to succeed academically. In addition, some interventions change a child’s construal; the assumption is that once people from low SES have a foundation in the skills and structural resources needed to succeed, changing the construal of their experience can effectively reduce the achievement gap.

A bivariate analysis showed significant correlations (p <0.05, adjusted for multiple comparisons) of growth indices, and of rates of diarrheal and respiratory illnesses in infancy, with all the cognitive scores examined, except the PSI. However, most of these associations were attenuated after adjustment for SES. The WAZ score at age 10–14 months remained positively associated with the VCI score in a multivariable model. Similarly, Pinkerton et al reported positive cognitive development among Brazilian children aged 8.5 years in relation to their WAZ score at age 24 months. These findings emphasize the importance of maintaining good physical growth in infancy, which likely has long-term impact on children’s health and cognitive development.
The rate of respiratory illnesses was negatively associated with the PRI score in an SES-adjusted model. This finding concurs with studies that showed negative associations of aspects of physical health, as measured by lower respiratory tract infection or by burden of illness with cognitive development. However, the exact mechanisms of such associations remain to be elucidated. Interestingly, several studies have suggested that enteric infections and diarrheal diseases, especially in infancy, may have long-term impact on children’s cognitive development. In our analysis, no significant association of diarrheal diseases with cognitive development was found in models that adjusted for SES and WAZ; this corroborates a previous report.

Birthweight was positively correlated with the FSIQ and PRI scores, although the participants of our study were born at a gestational age of >34 weeks and birth weight >2000 gram. This finding highlights the importance of the prenatal life stage of generally healthy babies in shaping cognitive development through preadolescence. Other studies also showed lower cognitive scores among children born at late preterm (34–36 weeks) and early term (37–38 weeks) compared to full term (38–40 weeks).

While compelling evidence exists on the impact of breastfeeding and feeding practices in early childhood on cognitive development, feeding practices in infancy were not associated with cognitive development at preadolescence in this cohort. This might be explained by near universal breastfeeding in this population, and generally similar infant feeding practices in the community.

Our study has limitations. Although we were able to successfully contact 88.8% of the original cohort, some families refused to participate, which they mostly explained by lack of time. Moreover, some participants did not present to the cognitive assessment visit despite
multiple invitations. Nonetheless, baseline characteristics were similar between children who performed the cognitive assessment and the entire cohort. Strengths of the study include the longitudinal design from infancy to preadolescence, and the assessment of the exposure variables via medical records and maternal interviews from infancy. The cognitive assessment was performed by a validated test in Arabic (WISC®-IV) by two trained psychologists in child development. Our assessments of global cognitive function and multiple specific cognitive domains provide a comprehensive evaluation of the studied associations.

**Conclusions**

SES has strong direct long-term impact on overall cognitive development and on specific cognitive domains. Birthweight, weight indicators and respiratory illness in infancy might have long-term effects on children’s cognitive development through preadolescence. Children from economically disadvantaged communities should be targeted for reducing gaps in child health and adult health-inequalities.
Conflict of interest statement

All authors declare no conflicts of interest.

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Authors’ contributions


Availability of data and material

Individual level data cannot be publicly available. Aggregative data might be provided upon a reasonable request to the corresponding author.
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**Figure legends**

**Figure 1** Flow chart of enrollment of the study participants.

**Figure 2** Correlations between early-life exposures and cognitive scores at school age.*

*Bold italics* *p* < 0.05 after correction for multiple comparisons using the Benjamini-Hochberg false discovery rate method

FSIQ: full-scale intelligence quotient; g: grams; HAZ: height for age Z score; PRI: perceptual reasoning index; PSI: processing speed index; SES: socioeconomic status; VCI: verbal comprehension index; WAZ: weight for age Z score; WHZ: weight for age Z score; WMI: working memory index.

Spearman’s correlation coefficient was applied. Red represents negative correlations; green represents positive correlations; yellow and orange represent no/weak correlations (coefficient around 0).

**Figure 3** Correlations between SES, growth indicators and morbidity.*

*Bold italics* *p* < 0.05 after correction for multiple comparisons using the Benjamini-Hochberg false discovery rate method. HAZ: height for age Z score; SES: socioeconomic status; WAZ: weight for age Z score. Spearman’s correlation coefficient was applied.

Red/orange represents negative correlations; green represents positive correlations; yellow represents no/weak correlations (coefficient around 0).

**Supplementary Figure 1** Selected early-life exposures compared between participants of the entire cohort (n = 233) who took part in the infancy study and participants of the current (preadolescence) sample (n = 146).
A: Dietary practices at recruitment at baseline (ages 1–9 weeks) in 2006–2007; B: Duration of breastfeeding (months); C: Birth weight (grams); D: Gestational age at birth (weeks). The data presented are percentages of the total.

Supplementary Figure 2 mean cognitive scores determined by WISC-IV by sex.

The bars represent means and the error bars represent 95% confidence intervals. After correction for multiple comparisons using the Benjamini-Hochberg false discovery rate method, no significant differences were found between boys and girls in cognitive scores, except for the PSI score, \( *p = 0.001 \)

FSIQ: full scale intelligence quotient; PRI: perceptual reasoning index; PSI: processing speed index; VCI: verbal comprehension index; WMI: working memory index
Table 1: Early-life exposures compared between members of the entire cohort who took part in the infancy study and participants of the preadolescence assessment

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort n=233</th>
<th>Study sample n=146</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of maternal schooling years, mean (SD)</td>
<td>10.6 (3.4)</td>
<td>10.5 (3.6)</td>
</tr>
<tr>
<td>Number of paternal schooling years, mean (SD)</td>
<td>10.3 (3.5)</td>
<td>10.1 (3.6)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>131 (56.2%)</td>
<td>85 (58.2%)</td>
</tr>
<tr>
<td>Residential village, low SES, n (%)</td>
<td>134 (57.5%)</td>
<td>92 (63.0%)</td>
</tr>
<tr>
<td>Birthweight, mean (SD), gram</td>
<td>3256 (438)</td>
<td>3263 (434)</td>
</tr>
<tr>
<td>Gestational age at birth, mean (SD), weeks</td>
<td>39.1 (1.4)</td>
<td>39.1 (1.3)</td>
</tr>
<tr>
<td>Any breast feeding, n (%)</td>
<td>228 (97.9%)</td>
<td>144 (98.6%)</td>
</tr>
<tr>
<td>Received formula, n (%)</td>
<td>211 (91.3%)</td>
<td>128 (88.9%)</td>
</tr>
<tr>
<td>Received herbal tea, n (%)</td>
<td>226 (97.4%)</td>
<td>141 (97.2%)</td>
</tr>
<tr>
<td>Duration of breast feeding, mean (SD), months</td>
<td>6.8 (5.5)</td>
<td>6.7 (5.3)</td>
</tr>
<tr>
<td>Age of introducing formula, mean (SD), months</td>
<td>1.9 (1.4)</td>
<td>1.9 (1.3)</td>
</tr>
<tr>
<td>Age of introducing solid food, mean (SD), months</td>
<td>5.1 (1.3)</td>
<td>5.0 (1.2)</td>
</tr>
<tr>
<td>Mean HAZ (SD), (age 10-14 months)</td>
<td>-0.12 (1.08)</td>
<td>-0.14 (1.15)</td>
</tr>
<tr>
<td>Mean WAZ (SD), (age 10-14 months)</td>
<td>0.55 (1.13)</td>
<td>0.51 (1.17)</td>
</tr>
<tr>
<td>Mean WHZ (SD), (age 10-14 months)</td>
<td>0.78 (1.11)</td>
<td>0.74 (1.13)</td>
</tr>
<tr>
<td>Hemoglobin level, g/dL (age 9-18 months)</td>
<td>11.4 (0.9)</td>
<td>11.4 (0.8)</td>
</tr>
</tbody>
</table>

Data on these variables were obtained in the framework of the baseline assessment in infancy.

HAZ: height for age Z score; SD: standard deviation; SES: socioeconomic status;

WAZ: weight for age Z score; WHZ: weight for height Z score.
Table 2: Multivariable linear regression models of associations between early life exposures and cognitive scores at preadolescence

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Adjusted R²</th>
<th>ANOVA, F</th>
<th>P value</th>
<th>Independent variables</th>
<th>Beta coefficient (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FSIQ score</strong></td>
<td>0.333</td>
<td>16.8</td>
<td>&lt;0.001</td>
<td>SES score</td>
<td>8.2 (5.8, 10.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rate of respiratory episodes at age 2-18 months *</td>
<td>-3.1 (-7.4, 1.2)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Birthweight †</td>
<td>17.3 (0.91, 33.7)</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WAZ age 10-14 months</td>
<td>1.7 (-0.3, 3.6)</td>
<td>0.089</td>
</tr>
<tr>
<td><strong>VCI score</strong></td>
<td>0.327</td>
<td>16.4</td>
<td>&lt;0.001</td>
<td>SES score</td>
<td>7.4 (5.2, 9.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rate of respiratory episodes at age 2-18 months *</td>
<td>1.9 (-5.9, 2.0)</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Birthweight †</td>
<td>14.7 (-0.4, 29.8)</td>
<td>0.057</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WAZ age 10-14 months</td>
<td>2.2 (0.4, 4.0)</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>PRI score</strong></td>
<td>0.332</td>
<td>16.7</td>
<td>&lt;0.001</td>
<td>SES score</td>
<td>8.9 (6.2, 11.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rate of respiratory episodes at age 2-18 months *</td>
<td>-4.8 (-9.6, 0.01)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Birthweight †</td>
<td>29.6 (11.4, 48.9)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WAZ age 10-14 months</td>
<td>-0.4 (-2.5, 1.8)</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>WMI score</strong></td>
<td>0.071</td>
<td>3.6</td>
<td>0.011</td>
<td>SES score</td>
<td>4.3 (1.6, 6.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rate of respiratory episodes at age 2-18 months *</td>
<td>-3.5 (-8.5, 1.6)</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Birthweight †</td>
<td>9.4 (-9.8, 28.7)</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WAZ age 10-14 months</td>
<td>0.7 (-1.6, 3.0)</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>PSI score</strong></td>
<td>0.187</td>
<td>6.8</td>
<td>&lt;0.001</td>
<td>SES score</td>
<td>6.2 (3.1, 9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rate of respiratory episodes at age 2-18 months *</td>
<td>1.2 (-4.3, 6.7)</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Birthweight †</td>
<td>19.4 (-1.8, 40.5)</td>
<td>0.073</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WAZ age 10-14 months</td>
<td>1.8 (-0.8, 4.3)</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sex</td>
<td>9.3 (3.7, 15.0)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

FSIQ: Full-scale intelligence quotient; PRI: perceptual reasoning index; PSI: processing speed index; SES: socioeconomic status; VCI: verbal comprehension index; WAZ: weight for age Z score; WMI: working memory index. * Natural logarithm transformation
<table>
<thead>
<tr>
<th></th>
<th>IQ</th>
<th>VCI</th>
<th>PRI</th>
<th>WMI</th>
<th>PSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SES composite index</td>
<td>0.52</td>
<td>0.50</td>
<td>0.55</td>
<td>0.30</td>
<td>0.33</td>
</tr>
<tr>
<td>HAZ at age 10-14 months</td>
<td>0.25</td>
<td>0.29</td>
<td>0.20</td>
<td>0.13</td>
<td>0.18</td>
</tr>
<tr>
<td>WAZ at age 10-14 months</td>
<td>0.21</td>
<td>0.26</td>
<td>0.10</td>
<td>0.10</td>
<td>0.23</td>
</tr>
<tr>
<td>WHZ at age 10-14 months</td>
<td>0.09</td>
<td>0.13</td>
<td>-0.02</td>
<td>0.02</td>
<td>0.17</td>
</tr>
<tr>
<td>Gestational age at birth, weeks</td>
<td>0.14</td>
<td>0.20</td>
<td>0.11</td>
<td>0.04</td>
<td>0.12</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>0.10</td>
<td>0.11</td>
<td>0.12</td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Duration of breastfeeding</td>
<td>0.10</td>
<td>0.10</td>
<td>0.06</td>
<td>0.11</td>
<td>-0.01</td>
</tr>
<tr>
<td>Child’s age at introducing formula (months)</td>
<td>0.05</td>
<td>0.04</td>
<td>0.01</td>
<td>0.07</td>
<td>0.09</td>
</tr>
<tr>
<td>Hemoglobin, age 9-18 months</td>
<td>0.02</td>
<td>0.11</td>
<td>-0.02</td>
<td>-0.05</td>
<td>-0.06</td>
</tr>
<tr>
<td>Child’s age at introducing solid foods (months)</td>
<td>-0.16</td>
<td>-0.17</td>
<td>-0.09</td>
<td>-0.16</td>
<td>-0.06</td>
</tr>
<tr>
<td>Rate of respiratory episodes, age 2-18 months</td>
<td>-0.31</td>
<td>-0.34</td>
<td>-0.32</td>
<td>-0.25</td>
<td>-0.15</td>
</tr>
<tr>
<td>Rate of diarrhea episodes, age 2-18 months</td>
<td>-0.34</td>
<td>-0.32</td>
<td>-0.36</td>
<td>-0.24</td>
<td>-0.21</td>
</tr>
</tbody>
</table>
Figure 1: Flow chart of enrollment of the study participants

Candidate children
n=233

- Successful contact
  n=207 (88.8%)

- Refused
  n=18 (8.7%)
  Enrolled but withdrew later
  n=15 (7.2%)

- Not found
  n=24 (10.3%)
  Special education
  n=2 (0.9%)

- Enrolled
  n=174 (84.1%)

- Completed cognitive assessment
  n=146 (83.9%)
<table>
<thead>
<tr>
<th></th>
<th>SES composite index</th>
<th>HAZ at age 10-14 months</th>
<th>WAZ at age 10-14 months</th>
<th>Rate of respiratory episodes, age 2-18 months</th>
<th>Rate of diarrhea episodes, age 2-18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAZ at age 10-14 months</td>
<td>0.17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAZ at age 10-14 months</td>
<td>0.05</td>
<td>0.72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of respiratory episodes, age 2-18 months</td>
<td>-0.33</td>
<td>-0.20</td>
<td>-0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of diarrhea episodes, age 2-18 months</td>
<td>-0.48</td>
<td>-0.21</td>
<td>-0.07</td>
<td>0.33</td>
<td></td>
</tr>
</tbody>
</table>