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# Association between chest-to-head circumference ratio at birth and childhood neurodevelopment: the Japan Environment and Children's Study

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## Original Article

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**Abstract**

Children born growth-restricted are well recognized to be at an increased risk of poor neurodevelopmental outcomes. This prospective study examined the influence of chest-to-head circumference ratio at birth on neurodevelopment in the first three years among children enrolled in the Japan Environment and Children's Study. We analyzed information of 84,311 children (43,217 boys, 41,094 girls). Children were divided into low, normal, and high chest-to-head circumference ratio groups. Neurodevelopment was assessed every six months (from 6 months to 3 years) using the Ages and Stages Questionnaire (Japanese translation), with delays defined as scores below 2 standard deviations from the mean. Additionally, we evaluated the contributions of chest and head circumference to the observed association. Linear mixed-effect regression revealed increased risk of delays in communication, gross motor, fine motor, problem-solving, and personal-social skills in the low-ratio group compared to the normal-ratio group. Adjusted risk ratios were in the range of 1.14 – 1.39 in boys and 1.16 – 1.37 in girls, with no such increase observed in the high-ratio group. The heightened risk in the low-ratio group was likely associated with a relatively narrow chest rather than a large head. The area under the ROC curves in predicting any developmental delay at three years for newborn measurements ranged from 0.513 to 0.526 in boys and 0.509 to 0.531 in girls. These findings suggest that a low chest-to-head circumference ratio may indicate children who are at risk for neurodevelopmental deficits. However, the ability to predict poor neurodevelopmental outcomes at three years of age is limited.

## Introduction

Children who exhibit delayed psychomotor development in early childhood (e.g., delays in motor function or language ability) often continue to show developmental deficits or psychological disorders in late childhood and even adulthood.[1,2] Early intervention improves functioning in such children;[3,4]therefore, it is important to recognize early the children who are at risk of poor psychomotor development.

Children born preterm[5] or growth-restricted[6] are well recognized to be at an increased risk of poor neurodevelopmental outcomes, making them targets for surveillance and intervention. Preterm children are defined as those born before 37 weeks of gestation. Fetuses with abdominal circumference or estimated fetal weight below the 3rd percentile are considered growth-restricted, whereas those between the 3rd and 10th percentile could be either normal or growth-restricted, depending on additional evidence of placental insufficiency, such as umbilical artery or uterine artery Doppler results.[7] However, it is important to note that some children born at term or despite having a birthweight above the 10th percentile may have experienced pathological growth restriction *in utero* and may also require monitoring.

Head circumference, a surrogate for brain size, has been extensively studied and identified as a factor in various neurodevelopmental outcomes.[8–12] In contrast, few studies[13] have examined the effect of chest circumference on neurodevelopmental outcomes in children. Similarly, body disproportionality, an indicator of *in utero* growth impairment,[14] is thought to influence children neurodevelopment but has received limited empirical attention.[15]

Recently, we investigated how chest-to-head circumference ratio at birth influences obstetric and neonatal outcomes using data from the Japan Environment and Children's Study (JECS), a nationwide birth cohort.[16] We found that, regardless of gestational age and birthweight, the rate

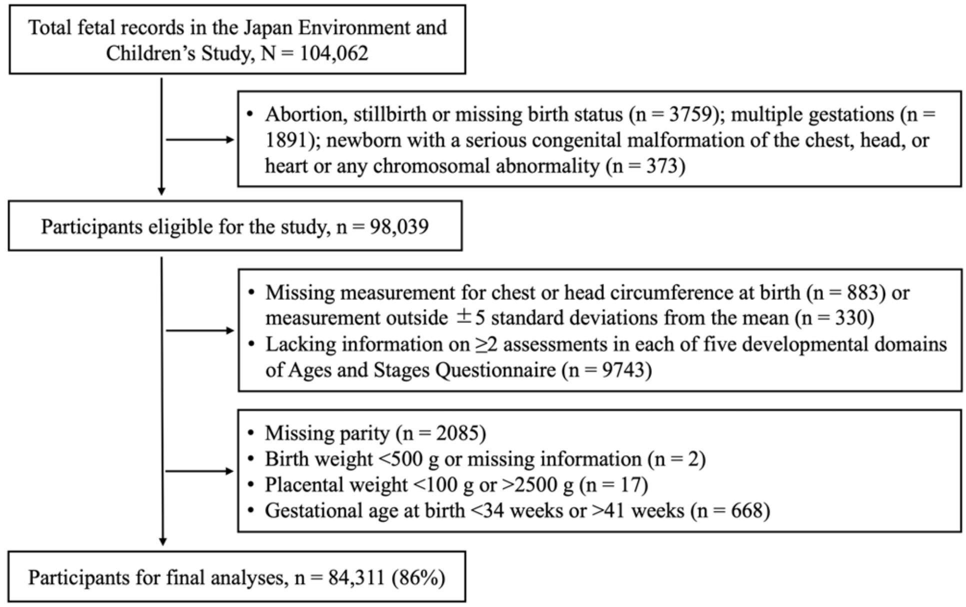


**Figure 1.** Summary of participant selection.

of adverse outcomes—such as cesarean delivery, Apgar score <7 at 5 min, respiratory complications, and prolonged hospitalization—was significantly higher with a chest-to-head circumference ratio below the 10th percentile and lower with a ratio above the 90th percentile compared with a ratio between the 10th and 90th percentile of the cohort distribution. This suggests that a low chest-to-head circumference ratio at birth may indicate suboptimal *in utero* development. Newborns with a low ratio may have experienced some form of intrauterine insult, the effects of which persist into the neonatal period; however, it remains unclear whether these effects extend beyond the neonatal stage and influence a child's neurodevelopment.

In this study, we examined the rate of psychomotor delays over time and determined the risk of such delays with a low or high chest-to-head circumference ratio at birth relative to the normal ratio during the first 3 years of life among children enrolled in the JECS. We hypothesized that children born with a low ratio are at greater risk of psychomotor delays, whereas those with a high ratio are at lower risk. Additionally, since focusing solely on the chest-to-head circumference ratio might overlook the predictive value of individual measurements, we also investigated how chest circumference and head circumference independently predict childhood neurodevelopment.

## Methods

### Study design and participants

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. In this prospective observational study, we used the "jecs-ta-20190930" dataset (released October 2019) from the JECS. Pregnant women throughout Japan were recruited between January 2011 and March 2014, and approximately 100,000 pregnancies were registered. Participant information and details of pregnancy and delivery were collected through standardized questionnaires (distributed during the first trimester, during the second or third trimester, at one month postnatal, and every 6 months thereafter) or from medical records (retrieved during the first trimester and at birth). The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (No.100910001) and the ethics committees of all participating institutions. Written informed consent was obtained from all participants. The detailed protocol and baseline information of the participants can be found elsewhere.[17,18]

The "jecs-ta-20190930" dataset comprises 104,062 fetal records (Fig. 1). The current study was restricted to live-born singletons without a serious congenital malformation of the chest, head, or heart, or any chromosomal abnormality. Of the remaining 98,039 eligible records, we excluded records that were missing measurements of chest or head circumference and those with values above or below 5 standard deviations from the means (i.e., outliers). Also excluded were those who lacked psychomotor assessment information for at least 2 time points (from a total of 6 assessments) in each of 5 developmental domains. Finally, we excluded records that were missing data on parity status, had a birthweight <500 g or missing, a placental weight <100 g or >2500 g, and those in which the child's gestational age was <34 weeks or >41 weeks. A total of 84,311 records were included in the final analyses.

### Chest-to-head circumference ratio at birth

Newborn chest-to-head circumference ratio was calculated as (chest circumference/head circumference) × 100. Chest and head circumference measurements were transcribed from the medical records. These measurements are routinely performed at birth by a midwife following standardized procedures to detect any serious abnormalities. On a calm newborn, head circumference is measured along the line passing the glabella and the external occipital protuberance, and the chest circumference is measured on the nipple line perpendicular to the body axis. Both measurements are recorded to the nearest 0.1 cm using a non-stretchable tape.

### Psychomotor assessment

Psychomotor development was prospectively assessed at 6, 12, 18, 24, 30, and 36 months through postal surveys using the

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age-appropriate Japanese translation of the Ages and Stages Questionnaire (ASQ), Third Edition.[19] The ASQ is a caregiver-completed developmental screening tool consisting of 21 questionnaires designed for children aged 1 to 66 months. Each ASQ contains 30 questions covering 5 developmental domains (6 questions per domain): communication, gross motor, fine motor, problem-solving, and personal-social. For each question, the caregiver reports "yes" (= 10 points, the child performs the activity), "sometimes" (= 5 points, the child occasionally performs the activity), or "not yet" (= 0 points, the child has not performed the activity), resulting in domain scores ranging from 0 to 60. Higher scores reflect greater skill levels.

Mezawa et al. proposed cutoff scores for the Japanese version of ASQ-3.[19] They found that for nearly all domains in children under 2 years, the Japanese cutoffs were more than 5 points lower than those in the original ASQ-3, suggesting slower development in Japanese children compared to their US counterparts. However, we noted that their study included children from limited geographical areas, with a relatively higher proportion of preterm infants (7.5%) and low-birthweight infants (12.1%) compared to our study (3.5% preterm and 7.0% low birthweight). In our study, we classified children as having a developmental delay in a specific domain if their score fell more than 2 standard deviations (SD) below the mean for that domain, based on our large nationwide dataset. The cutoff scores (i.e., score <2 SD from the mean) for the original ASQ-3, the Japanese study, and our study are presented in Supplementary Table S1. We observed that cutoff scores from the Japanese study and our population were largely comparable, except for the communication, gross motor, and problem-solving domains at 6 months, and the communication domain at 1 year, where differences exceeded 5 points.

## Potential confounders and covariates

Based on the literature[5,20–25] and considering causal relationships between exposure and outcome variables, we examined the following variables as covariates and potential confounders: geographic region at the time of recruitment, parental age (≤24, 25 – 34, ≥35 years), parental education (high school or less, vocational school/college, or university or higher), and gestational age at birth (week). Additionally, we included maternal pre-pregnancy body mass index (BMI: <18.5, 18.5 – 24.9, ≥25 kg/m$^2$), parity (nulliparous or multiparous), iodine intake during pregnancy (tertiles of intake in micrograms per day), and maternal tobacco and alcohol use during pregnancy (never, former, current). We also considered the presence of hypertension (preexisting or pregnancy-induced), diabetes mellitus (preexisting or gestational), antenatal epilepsy, mental health conditions (depression, anxiety disorders, and schizophrenia), psychological distress, TORCH infections during pregnancy (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and syphilis. Due to high rate of missing data, this information was not adjusted in risk estimation.), and the presence of chorioamnionitis. The use of steroids and psychotropic medication during pregnancy (SSRIs, SNRIs, tricyclic antidepressants, valproic acid, phenobarbital, carbamazepine, and lithium carbonate) was also evaluated.

A recent nationwide study on iodine nutrition reported the median urinary iodine concentration (UIC) values for school-aged children across various geographic regions in Japan.[26] Based on this data, we categorized the regions into three groups for our study: Group 1 (UIC 200 – 249 μg/L), which includes Koshin, Aichi, Fukuoka, Southern Kyushu, and Okinawa; Group 2 (UIC 250 – 299 μg/L), which includes Miyagi, Fukushima, Chiba, Kanagawa, Kyoto, Osaka, Hyogo, Tottori, and Kochi; and Group 3 (UIC ≥300 μg/L), which includes Hokkaido and Toyama. While individual iodine intake during pregnancy was considered a defining exposure, the UIC-based classification of geographic regions reflects broader regional iodine nutrition characteristics at the time of recruitment. Maternal psychological distress was assessed using the Japanese version of six-item Kessler Psychological Distress Scale (K6) during mid-pregnancy (median: 27.0 weeks of gestation), with scores ≥5 indicating distress.[24,27] Gestational age was established using the first trimester ultrasound examination or estimated from self-reported date of the last menstrual period.

## Statistical analysis

Children were divided into 3 groups by individual chest-to-head circumference ratio at birth: low ratio (<10th percentiles), normal ratio, or high ratio (>90th percentiles) using an internal reference.[16] This gestational age-, sex-, and parity-specific reference chart for chest-to-head circumference ratio was constructed using the JECS population of 93,904 non-anomalous singletons live-born at $34^{0/7}$ – $42^{6/7}$ weeks' gestation.[16] We determined the rate and risk of delays over time for each of the groups by using Poisson regression with a robust error variance. Around 8%, 11%, 16%, 12%, 15%, and 13% of children had missing information for each developmental domain assessed at 6, 12, 18, 24, 30, and 36 months, respectively (Supplementary Table S2). Therefore, we chose linear mixed-effects models, which can handle incomplete outcome data, to estimate crude and adjusted risks of delays for the low- and high-ratio groups relative to the normal-ratio group during the first 3 years.[28] The models used group and time as fixed covariates. We included random effects at the individual level, accounting for heterogeneity in development over time and at baseline (6 months of age), with random slopes and intercepts, respectively. Since boys and girls develop at different rates,[20,29] we analyzed the population stratified by sex of the child. We did not attempt any statistical method, such as multiple imputation, to evaluate sensitivity to missing data because only a small percentage of participants had missing information on covariates (Table 1), and we used linear mixed-effects models in the risk estimation.

Considering that some children born at term or with a birthweight above the 10th percentile may experience pathological growth restriction and that indications for a cesarean delivery could also potentially influence psychomotor development, additional analyses were conducted. These analyses explored the risk of delays in a lower-risk population comprising 62,308 children who were not small-for-gestational-age and were delivered vaginally at or after the 37th week of gestation.

Furthermore, we studied how chest circumference and head circumference individually contribute to neurodevelopment in children. Pearson's correlation coefficients were utilized to determine the correlations among newborn measurements (in absolute values). We standardized chest circumference, head circumference, and birthweight measurements into $z$-scores, categorizing them as <10th percentile for low measurements, 10th – 90th percentile for normal measurements, and >90th percentile for high measurements. Associations between individual measurements, including chest-to-head circumference ratio, and delayed development were evaluated. Finally, we determined the predictability of each anthropometric measurement for any

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**Table 1.** Characteristics of the study population according to chest-to-head circumference ratio

| Characteristic | All ($N = 84,311$) | Low ($n = 9939$) | Normal ($n = 68,276$) | High ($n = 6096$) | *p*-value[a] |
|---|---|---|---|---|---|
| | Mean (SD) or number (%) | | | | |
| **Maternal information** | | | | | |
| Geographic regions at recruitment[b] | | | | | <0.001 |
| Group 1 | 21,701 (25.7) | 2183 (22.0) | 17,595 (25.8) | 1923 (31.6) | |
| Group 2 | 51,411 (61.0) | 6409 (64.5) | 41,605 (60.9) | 3397 (55.7) | |
| Group 3 | 11,199 (13.3) | 1347 (13.6) | 9076 (13.3) | 776 (12.7) | |
| Age category | | | | | <0.001 |
| ≤ 24 y | 7564 (9.0) | 747 (7.5) | 6,217 (9.1) | 600 (9.8) | |
| 25 – 34 y | 53,524 (63.5) | 6195 (62.3) | 43,426 (63.6) | 3903 (64.0) | |
| ≥35 y | 23,220 (27.5) | 2996 (30.1) | 18,631 (27.3) | 1593 (26.1) | |
| Missing | 3 (0.0) | 1 (0.0) | 2 (0.0) | 0 (0.0) | |
| Parity | | | | | 0.449 |
| Nulliparous | 34,753 (41.2) | 4069 (40.9) | 28,128 (41.2) | 2556 (41.9) | |
| Multiparous | 49,558 (58.8) | 5870 (59.1) | 40,148 (58.8) | 3540 (58.1) | |
| Pre-pregnancy BMI | | | | | <0.001 |
| <18.5 kg/m$^2$ | 13,608 (16.1) | 1820 (18.3) | 10,971 (16.1) | 817 (13.4) | |
| 18.5 – 24.9 kg/m$^2$ | 62,067 (73.6) | 7193 (72.4) | 50,351 (73.8) | 4523 (74.2) | |
| ≥25 kg/m$^2$ | 8594 (10.2) | 924 (9.3) | 6916 (10.1) | 754 (12.4) | |
| Missing | 42 (0.1) | 2 (0.0) | 38 (0.1) | 2 (0.0) | |
| Education | | | | | 0.013 |
| High school or less | 29,220 (34.7) | 3363 (33.8) | 23,739 (34.8) | 2118 (34.7) | |
| Vocational school/College | 35,549 (42.2) | 4158 (41.8) | 28,766 (42.1) | 2625 (43.1) | |
| University or higher | 18,618 (22.1) | 2306 (23.2) | 15,033 (22.0) | 1279 (21.0) | |
| Missing | 924 (1.1) | 112 (1.1) | 738 (1.1) | 74 (1.2) | |
| Tobacco use during pregnancy | | | | | 0.121 |
| Never | 49,577 (58.8) | 5863 (59.0) | 40,148 (58.8) | 3566 (58.5) | |
| Former | 30,270 (35.9) | 3500 (35.2) | 24,558 (36.0) | 2212 (36.3) | |
| Current | 3450 (4.1) | 450 (4.5) | 2746 (4.0) | 254 (4.2) | |
| Missing | 1014 (1.2) | 126 (1.3) | 824 (1.2) | 64 (1.1) | |
| Alcohol consumption during pregnancy | | | | | 0.231 |
| Never | 29,025 (34.4) | 3421 (34.4) | 23,463 (34.4) | 2141 (35.1) | |
| Former | 46,059 (54.6) | 5378 (54.1) | 37,377 (54.7) | 3304 (54.2) | |
| Current | 8428 (10.0) | 1051 (10.6) | 6778 (9.9) | 599 (9.8) | |
| Missing | 799 (1.0) | 89 (0.9) | 658 (1.0) | 52 (0.9) | |
| Iodine intake during pregnancy, µg/day | | | | | 0.006 |
| 1st tertile | 27,638 (32.8) | 3099 (31.2) | 22,547 (33.0) | 1992 (32.7) | |
| 2nd tertile | 28,014 (33.2) | 3407 (34.3) | 22,598 (33.1) | 2009 (33.0) | |
| 3rd tertile | 28,150 (33.4) | 3376 (34.0) | 22,709 (33.3) | 2065 (33.9) | |
| Missing | 509 (0.6) | 57 (0.57) | 422 (0.62) | 30 (0.49) | |
| **Maternal clinical information during pregnancy** | | | | | |
| Hypertension[c] (yes) | 2779 (3.3) | 510 (5.1) | 2106 (3.1) | 163 (2.7) | <0.001 |
| Diabetes[d] (yes) | 2601 (3.1) | 327 (3.3) | 2083 (3.1) | 191 (3.1) | 0.425 |

(*Continued*)

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**Table 1.** (*Continued*)

| Characteristic | All (*N* = 84,311) | Low (*n* = 9939) | Normal (*n* = 68,276) | High (*n* = 6096) | *p*-value[a] |
|---|---|---|---|---|---|
| Graves' disease (yes) | 557 (0.66) | 80 (0.80) | 451 (0.66) | 26 (0.43) | 0.016 |
| Epilepsy (yes) | 204 (0.24) | 26 (0.26) | 159 (0.23) | 19 (0.31) | 0.445 |
| Mental health conditions[e] (yes) | 639 (0.76) | 79 (0.79) | 528 (0.77) | 32 (0.52) | 0.091 |
| Psychological distress[f] (yes) | 24,139 (28.6) | 2915 (29.3) | 19,450 (28.5) | 1774 (29.1) | 0.156 |
| TORCH infection[g] (yes) | 1927 (7.0) | 202 (6.1) | 1580 (7.1) | 145 (7.4) | 0.070 |
| Intrauterine infection (yes) | 453 (0.54) | 48 (0.48) | 366 (0.54) | 39 (0.64) | 0.417 |
| Steroid use (yes) | 2209 (2.6) | 281 (2.8) | 1798 (2.6) | 130 (2.1) | 0.025 |
| Psychotropic medication[h] (yes) | 883 (1.05) | 93 (0.94) | 705 (1.04) | 85 (1.4) | 0.016 |
| **Paternal information** | | | | | |
| Age category | | | | | <0.001 |
| ≤ 24 y | 3828 (4.5) | 393 (4.0) | 3121 (4.6) | 314 (5.2) | |
| 25 – 34 y | 42,717 (50.7) | 4857 (48.9) | 34,735 (50.9) | 3125 (51.3) | |
| ≥35 y | 34,797 (41.3) | 4344 (43.7) | 28,001 (41.0) | 2452 (40.2) | |
| Missing | 2969 (3.5) | 345 (3.5) | 2419 (3.5) | 205 (3.4) | |
| Education | | | | | 0.001 |
| High school or less | 35,788 (42.5) | 4128 (41.5) | 29,035 (42.5) | 2625 (43.1) | |
| Vocational school/College | 18,799 (22.3) | 2126 (21.4) | 15,306 (22.4) | 1367 (22.4) | |
| University or higher | 28,342 (33.6) | 3532 (35.5) | 22,807 (33.4) | 2003 (32.9) | |
| Missing | 1382 (1.6) | 153 (1.5) | 1128 (1.7) | 101 (1.7) | |
| **Child's information** | | | | | |
| Sex (boys) | 43,217 (51.3) | 5,075 (51.1) | 34,993 (51.3) | 3,149 (51.7) | 0.762 |
| Gestational age at birth, week | 38.9 (1.3) | 38.8 (1.3)† | 38.9 (1.3) | 39.0 (1.2)† | <0.001 |
| Birthweight, g | 3042.3 (382.7) | 2828.1 (377.2)† | 3056.6 (367.2) | 3231.8 (413.3)† | <0.001 |
| Placental weight, g | 560.5 (105.5) | 522.5 (103.8)† | 563.2 (103.6) | 592.5 (112.1)† | <0.001 |
| Birthweight-to-placental weight ratio | 5.5 (0.8) | 5.5 (0.9) | 5.5 (0.8) | 5.6 (0.8)* | 0.012 |
| Chest circumference, cm | 31.8 (1.6) | 30.2 (1.5)† | 31.9 (1.4) | 33.4 (1.5)† | <0.001 |
| Head circumference, cm | 33.2 (1.4) | 33.9 (1.4)† | 33.2 (1.3) | 32.4 (1.4)† | <0.001 |
| Chest-to-head circumference ratio[i] | 95.8 (4.0) | 89.1 (2.4) | 96.1 (2.7) | 103.2 (2.4) | |

[a]Results of Student's *t*-test or one-way ANOVA for continuous data and chi-squared test for categorical data.
[b]Categorized by median urinary iodine concentration (UIC): - Group 1: UIC 200 – 249 µg/L (Koshin, Aichi, Fukuoka, Southern Kyushu, and Okinawa)—Group 2: UIC 250 – 299 µg/L (Miyagi, Fukushima, Chiba, Kanagawa, Kyoto, Osaka, Hyogo, Tottori, and Kochi)—Group 3: UIC ≥300 µg/L (Hokkaido and Toyama).
[c]Presence of hypertensive disorders of pregnancy.
[d]Presence of type 2 diabetes or gestational diabetes.
[e]Presence of depression, anxiety disorders or schizophrenia.
[f]Assessed during mid-pregnancy using the Japanese version of six-item Kessler Psychological Distress Scale (K6) with scores≥5 indicating distress.
[g]Presence of toxoplasmosis, rubella, cytomegalovirus, herpes simplex or syphilis.
[h]The use of SSRIs, SNRIs, tricyclic antidepressants, valproic acid, phenobarbital, carbamazepine or lithium carbonate.
[i]Low, <10th percentile; normal, 10 – 90th percentile; high, >90th percentile.
*, $p < 0.05$ and †, $p < 0.001$: *p*-values from Bonferroni correction for multiple comparisons, compared to normal ratio group.

developmental delay at three years of age using the area under the receiver operating characteristic curves.

Differences in parental and neonatal characteristics among groups were analyzed using Student's *t*-test or one-way ANOVA (followed by the Bonferroni correction for multiple comparisons) for continuous data and the chi-squared test for categorical data. Moreover, we compared the characteristics of participants between those included in and excluded from the present study. Descriptive statistics are reported as mean (SD) for continuous data and number and proportion (%) for categorical data. A two-tailed *p*-value of <0.05 was considered statistically significant. Statistical analyses were performed using Stata/MP 18.0 software (StataCorp., College Station, Texas).

## Results

Of the 98,039 potentially eligible fetal records, we excluded 13,728 records according to predetermined criteria (Fig. 1). Mothers who were excluded were more likely to be younger (age 24 years or younger), have lower educational attainment, experience

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hypertension and psychological distress, and have missing information on education, alcohol or tobacco use, iodine intake, and adverse clinical conditions during pregnancy. Fathers who were excluded were more likely to have missing age and educational attainment information. Children who were excluded were more likely to have lower birthweight (Supplementary Table S3). Of the 84,311 children analyzed, 9939 (11.8%) and 6096 (7.2%) were classified as having a low and a high chest-to-head circumference ratio at birth, respectively. Using a cutoff score of <2 SD from the mean score for a given developmental domain, 8.2%, 16.0%, 12.1%, 16.4%, 18.3%, and 18.1% of boys and 7.7%, 12.8%, 9.2%, 11.1%, 8.7%, and 8.7% of girls had a delay in one or more developmental domain at 6, 12, 18, 24, 30, and 36 months, respectively.

Table 1 presents the characteristics of the study population based on chest-to-head circumference ratios. The groups differed significantly in geographic location at recruitment. Apart from a slightly higher proportion of mothers aged 35 years or older, those with a low pre-pregnancy body mass index, and those with hypertension in the low-ratio group, no clinically significant differences in parental characteristics were observed among the groups. Birthweight and placental weight varied proportionately across the groups with low, normal, and high chest-to-head circumference ratios; the mean birthweight was lowest in the low-ratio group and highest in the high-ratio group, reflecting a similar trend in placental weight. In addition, the ratio of birthweight-to-placental weight, serving as a proxy measure for fetal nutrition adequacy, remained consistent across the ratio groups.

### *Association between chest-to-head circumference ratio at birth and developmental delays*

In both sexes, the rate of screening positive for delays in motor function, personal-social skills, and communication was highest at 1, 2, and 2.5 years, respectively (Fig. 2). During the follow-up period, both males and females in the low-ratio group had significantly higher rates of delays in all developmental domains compared to the normal-ratio group. However, no significant differences were found in the rates of delays in the high-ratio group (Figs. 3 and 4, Supplementary Tables S4 and S5). In both sexes, a low ratio increased the risk of delay compared to a normal ratio, whereas a high ratio did not show any difference in the risk of delay in all developmental domains (Table 2). The increased risk for delayed development with a low ratio was also observed among the seemingly lower-risk population of children born not small-for-gestational-age and delivered vaginally at term, albeit to a lesser extent in gross and fine motor functions (Table 3).

### *Associations of chest circumference and head circumference at birth with developmental delays*

In the additional analyses, a robust correlation was observed between chest circumference and birthweight (Supplementary Table S6). Both measurements exhibited similar relationships with psychomotor development; a narrow chest or lighter birthweight increased the risk of developmental delays, whereas a broader chest or heavier birthweight reduced the risk, although these findings were not statistically significant (Table 4). Conversely, head circumference indicated an increased risk of delays both in cases of smaller size (<10th percentile) and larger size (>90th percentile), although statistical significance was not consistently evident in most domains (Table 4). The unadjusted association of low and high birthweight and circumferences of the chest and head with the risk of developmental delay in the lower-risk population of children is presented in Supplementary Table S7. Compared to analyses using the total population, the effect of low birthweight and chest circumference on developmental outcomes was attenuated, whereas the effect of a low head circumference was no longer observed. Table 5 shows the predictive capability of each newborn measurement, including chest-to-head circumference ratio, for any developmental delay at three years of age. The area under the receiver operating characteristic curves for newborn measurements ranged from 0.513 to 0.526 in boys and 0.509 to 0.531 in girls.

## Discussion

We followed the psychomotor development of children for the first three years of life, stratifying them based on their chest-to-head circumference ratio at birth. The results showed that a low ratio increased the risk of developmental delay in both boys and girls, even after controlling for several confounding factors, including gestational age. This effect is likely attributed to a relatively narrow chest rather than a large head. Additionally, the elevated risk associated with a low ratio was also evident among term, non-small-for-gestational-age children. Furthermore, a reduced chest-to-head circumference ratio posed a greater risk for girls than for boys in terms of communication and personal-social conduct.

Our findings strongly suggest that although a child born with a low chest-to-head circumference ratio might survive despite a suboptimal *in utero* environment, detrimental effects can continue to impact the child's neurodevelopment during childhood. Growth impairment *in utero* has been associated with pre- and postnatal structural alterations in the brain, and with short- and long-term neuropsychological consequences such as problems in motor skills, cognition, and memory.[30,31] A large Norwegian study reported an association between low placental weight and increased risk for cerebral palsy.[32] In a recent study, we also found that a placental weight<10th percentile of the cohort distribution increases the risk of developmental delay at 3 years of age.[33] In the present study, the mean placental weight and birthweight were significantly lower in the low-ratio group than in the other ratio groups. Growth of the placenta and fetus are highly correlated, and impairment in placental development impacts the development of fetal organs, including the brain.[34] Animal studies have shown that serotonin is crucial for early fetal forebrain development,[35] and placental allopregnanolone influences oligodendrocyte differentiation and myelination in the developing cerebellum.[36] In humans, disruptions of placental synthesis of neurotransmitters such as dopamine, norepinephrine, and serotonin are suggested to impair fetal brain development.[37,38] Our data suggest that the increased risk for poorer neurodevelopmental outcomes with a low chest-to-head circumference ratio is most likely due to altered brain structure secondary to chronic undersupply of the nutrients, oxygen, growth factors, and hormones required for normal development due to a small placenta.

A low chest-to-head circumference ratio might be due to either a relatively large head or a relatively narrow chest, whereas a high ratio could result from either a relatively small head or a relatively broad chest. In our analyses, newborn chest circumference and birthweight were strongly correlated. The predictive impacts of these two measurements on the neurodevelopmental outcomes were notably similar: there was an increased risk of delays in children with a narrow chest or lighter birthweight and a tendency toward reduced risk in those with a broader chest or heavier

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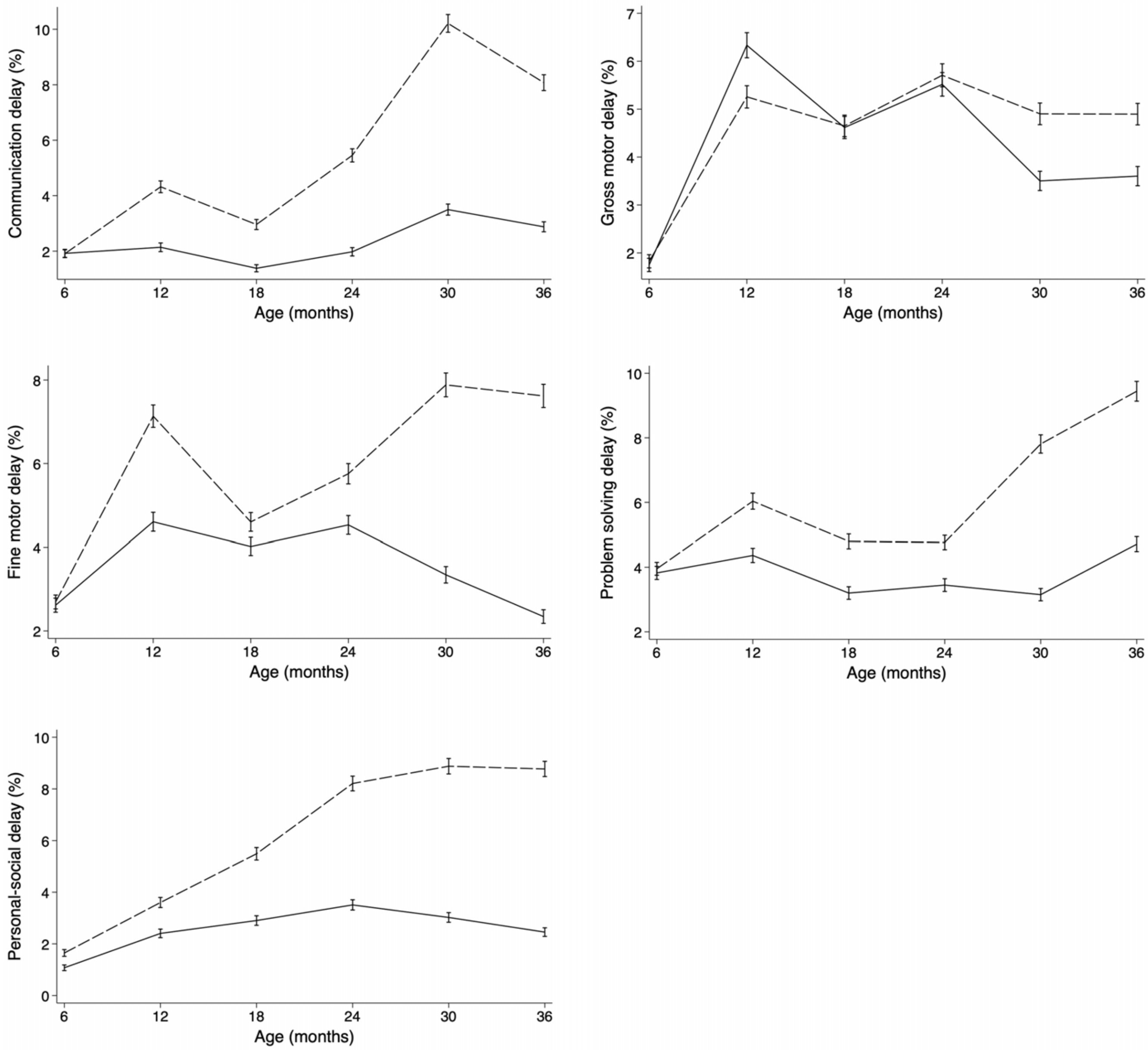


**Figure 2.** Rate of developmental delay from 6 to 36 months of age. Dashed and solid lines represent boys and girls, respectively. Error bars represent 95% confidence intervals.

birthweight. Conversely, head size indicated an increased risk of delays for both smaller circumference and larger circumference. Given the greater variation observed in chest circumference compared to head circumference, it is likely that the predictive ability of chest-to-head circumference ratio on childhood neurodevelopment is predominantly influenced by the variation in chest circumference. Specifically, it appears that a low ratio is more likely driven by a relatively narrow chest rather than a large head.

Head circumference is commonly used as a surrogate measurement of brain size and has been extensively investigated for its connection with childhood neurodevelopmental outcomes, but the findings remain inconsistent.[9,10,12,39] Several population studies have reported a positive association between head circumference at birth and childhood neurodevelopment.[10,39] Other have found varying association between greater head growth during infancy and different developmental outcomes in childhood.[12] However, Nicolaou and coworkers were unable to identify any association between head circumference or head growth during early childhood and neurodevelopmental outcomes.[9] In our study, we noted an elevated risk of developmental delays in cases with both smaller and larger head circumferences, although statistical significance was not consistently evident in most domains. However, it is crucial to highlight that the increased risk associated with a smaller head was no longer observed in the investigation among term, non-small-for-gestational-age children.

Interestingly, a reduced chest-to-head circumference ratio was found to affect psychomotor development differently in boys and girls. We observed that the negative impact of a low chest-to-head ratio was higher among girls for communication skills (adjusted risk ratio: 1.24 vs. 1.18 [girls vs. boys]) and personal-social conduct (1.28 vs. 1.16). We interpret these findings as reflecting a higher baseline risk for delayed development in boys compared to girls,

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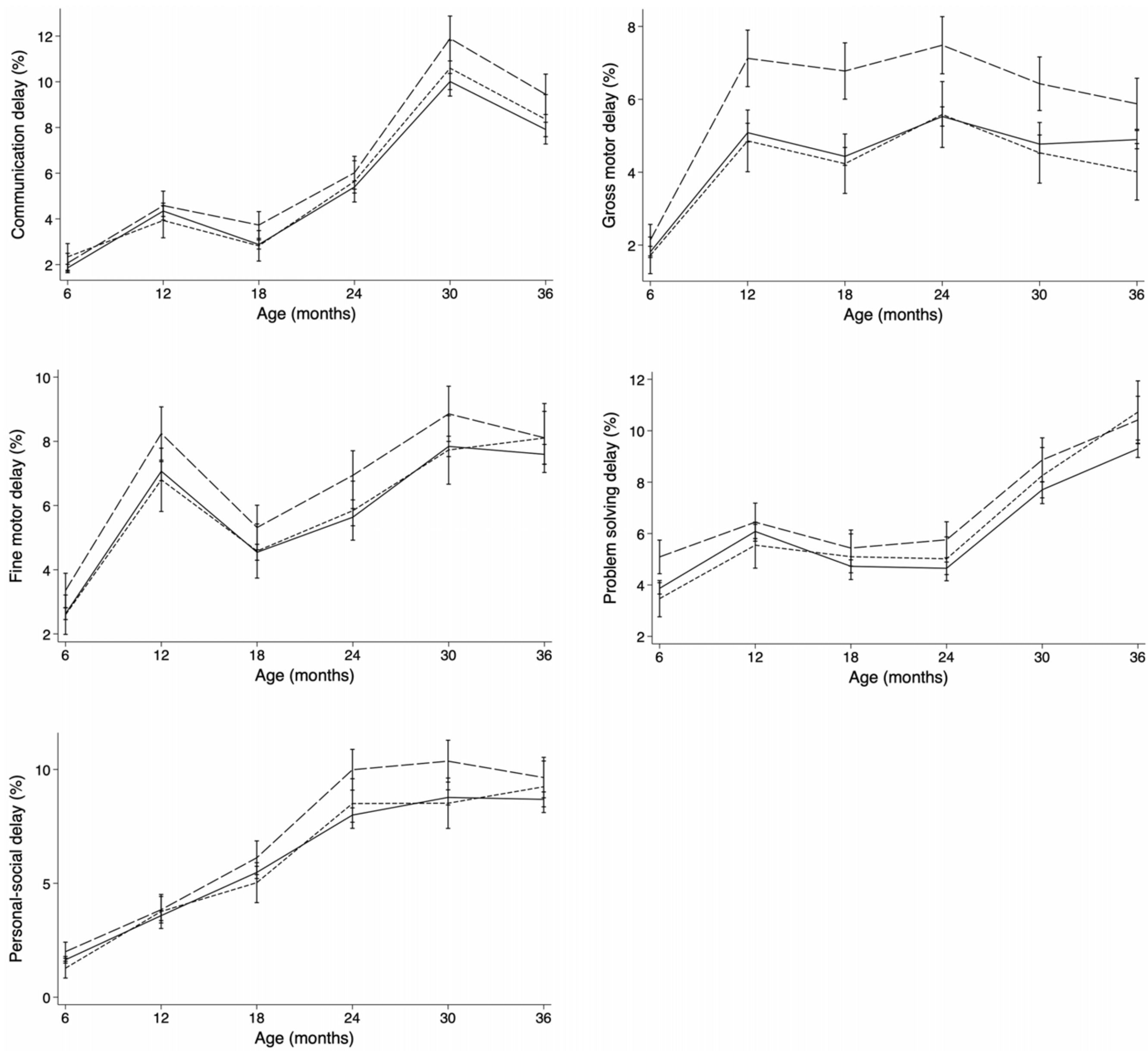


**Figure 3.** Rate of developmental delay from 6 to 36 months of age in three chest-to-head circumference ratio groups in boys. Long dashed, solid, and short dashed lines represent children with low, normal, and high chest-to-head circumference ratios, respectively. Error bars represent 95% confidence intervals.

which could explain why the additional risk associated with variations in chest-to-head circumference ratio was smaller in boys.

In our study, boys were more likely to screen positive for developmental delays compared to girls of the same age. Furthermore, girls who were affected showed relatively faster catch-up development in motor functions and personal-social conduct than boys. Sex differences have been reported in developmental scores for a given age and in the risk of developmental outcomes assessed with the ASQ.[23,40] Research suggests that these differences may be attributed to variation in neurodevelopmental physiology between boys and girls,[41] with boys generally acquiring developmental skills at a slower pace than girls.[20,29] However, it is also possible that the ASQ may exhibit inherent sex bias. We recommend further investigations into potential biases in the tool's design that could influence scores, as well as the establishment of sex-specific cutoffs or the evaluation of data stratified by sex.

### *Clinical implications*

The relative measure of chest size to head size at birth is grounded in the assumption that, in cases of placental insufficiency, fetal chest size varies more than head size due to brain-sparing. Our analyses revealed that head circumference exhibited less individual variation compared to chest circumference. Additionally, chest circumference showed a stronger correlation with birthweight, serving as a proxy for overall fetal growth. We found that a low chest-to-head circumference ratio was associated with an increased risk of developmental delays. Importantly, this effect was

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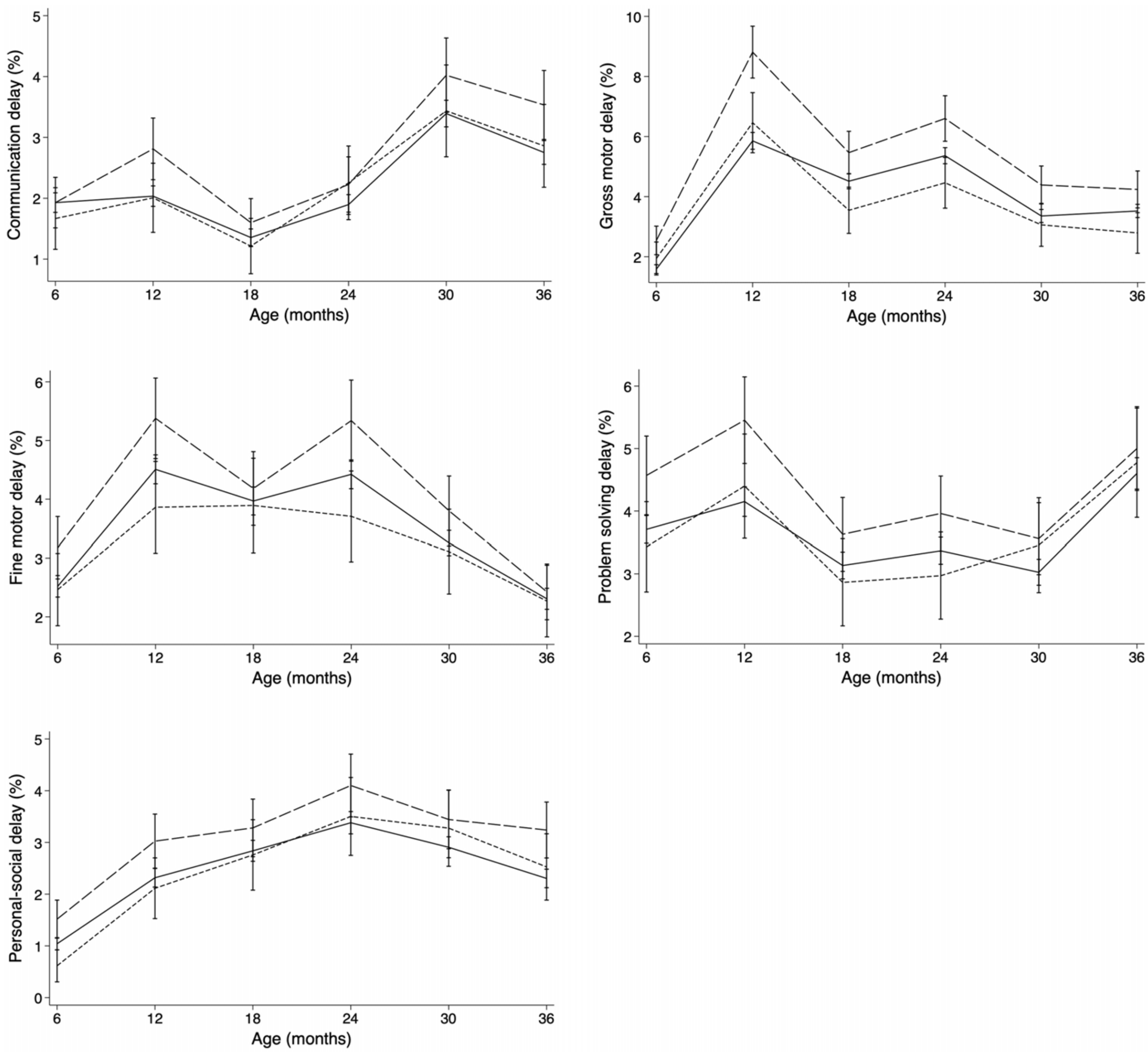


**Figure 4.** Rate of developmental delay from 6 to 36 months of age in three chest-to-head circumference ratio groups in girls. Long dashed, solid, and short dashed lines represent children with low, normal, and high chest-to-head circumference ratios, respectively. Error bars represent 95% confidence intervals.

independent of maternal age, education level, smoking status, iodine intake, pregnancy-related clinical conditions, maternal mental health, and psychotropic medication use during pregnancy. The elevated risk observed in term-born, non-small-for-gestational-age children suggests that the association is not due to immaturity from earlier gestation or low birthweight but rather to the persistent impact of intrauterine insults. Our current study, along with our previous research,[16] suggests that the chest-to-head circumference ratio at birth could help identify children who may require close medical attention, even if they are not classified as small-for-gestational-age or preterm. However, in the present study, none of the anthropometric fetal growth indicators, including the chest-to-head circumference ratio, adequately predicted neurodevelopmental outcomes in three-year-old children.

### *Strengths and limitations*

The ASQ has been validated in several countries and widely used in various birth cohort studies to screen for development delays. In the present study, we used a validated Japanese translation of the ASQ, Third Edition.[19] The cutoff scores derived from both the validation sample[19] and our population were largely comparable (Supplementary Table S1), indicating that the Japanese version of ASQ-3 is valid for use with Japanese children. The availability of a large number of records enabled us to adjust for several important factors, resulting in robust associations. However, residual confounding from antenatal maternal nutritional factors and parental developmental profiles remains a possibility. A primary limitation of this study was missing data for some ASQ assessments; however, we employed mixed-effects models capable

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**Table 2.** Risk of developmental delay in the first 3 years for children with low or high chest-to-head circumference ratio, relative to normal ratio

| | Low | | | High | | | Low | | | High | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | cRR | *z* | 95%CI | cRR | *z* | 95%CI | aRR | *z* | 95%CI | aRR | *z* | 95%CI |
| **Boys** | | | | | | | | | | | | |
| Communication | 1.22 | 4.63 | 1.12 – 1.33 | 1.02 | 0.34 | 0.91 – 1.14 | 1.18 | 3.60 | 1.08 – 1.29 | 1.04 | 0.65 | 0.93 – 1.17 |
| Gross motor | 1.45 | 8.59 | 1.33 – 1.58 | 0.90 | – 1.78 | 0.80 – 1.01 | 1.39 | 7.48 | 1.28 – 1.52 | 0.94 | – 0.93 | 0.83 – 1.07 |
| Fine motor | 1.19 | 4.94 | 1.11 – 1.28 | 0.98 | – 0.41 | 0.90 – 1.07 | 1.15 | 3.78 | 1.07 – 1.23 | 1.02 | 0.32 | 0.92 – 1.11 |
| Problem-solving | 1.19 | 4.69 | 1.10 – 1.27 | 1.01 | 0.24 | 0.92 – 1.11 | 1.14 | 3.57 | 1.06 – 1.23 | 1.05 | 1.01 | 0.96 – 1.15 |
| Personal-social | 1.19 | 4.84 | 1.11 – 1.28 | 0.96 | – 0.75 | 0.88 – 1.06 | 1.16 | 3.96 | 1.08 – 1.25 | 1.00 | 0.02 | 0.91 – 1.10 |
| **Girls** | | | | | | | | | | | | |
| Communication | 1.32 | 4.46 | 1.17 – 1.50 | 0.98 | – 0.26 | 0.83 – 1.15 | 1.24 | 3.25 | 1.09 – 1.41 | 1.01 | 0.16 | 0.85 – 1.21 |
| Gross motor | 1.44 | 8.25 | 1.32 – 1.57 | 0.90 | – 1.68 | 0.79 – 1.02 | 1.37 | 6.83 | 1.25 – 1.50 | 0.91 | – 1.48 | 0.79 – 1.03 |
| Fine motor | 1.22 | 4.41 | 1.12 – 1.33 | 0.95 | – 0.78 | 0.85 – 1.07 | 1.16 | 3.10 | 1.05 – 1.27 | 0.93 | – 1.16 | 0.82 – 1.05 |
| Problem-solving | 1.24 | 4.80 | 1.14–1.36 | 1.01 | 0.12 | 0.90 – 1.13 | 1.19 | 3.70 | 1.08 – 1.30 | 1.01 | 0.20 | 0.90 – 1.14 |
| Personal-social | 1.38 | 5.76 | 1.24 – 1.54 | 0.97 | – 0.35 | 0.84 – 1.13 | 1.28 | 4.26 | 1.14 – 1.43 | 1.01 | 0.09 | 0.86 – 1.18 |

Chest-to-head circumference ratio: low, <10th percentile; normal, 10th–90th percentile (reference group); high, >90th percentile of internally constructed growth chart.
aRR, adjusted risk ratio; cRR, crude risk ratio; 95%CI, 95% confidence interval.
Adjusted for parental age and educational status, maternal characteristics (geographic region at recruitment, parity, pre-pregnancy body mass index, iodine intake, and tobacco and alcohol use during pregnancy), as well as clinical conditions during pregnancy (hypertension, diabetes, Graves' disease, epilepsy, mental health conditions, psychological distress, infections during pregnancy, chorioamnionitis, and the use of steroids and psychotropic medications), along with gestational length.

**Table 3.** Risk of developmental delay in the first 3 years for children with low or high chest-to-head circumference ratio, relative to normal ratio in a lesser-risk population[a]

| | Low | | | High | | | Low | | | High | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | cRR | *z* | 95%CI | cRR | *z* | 95%CI | aRR | *z* | 95%CI | aRR | *z* | 95%CI |
| **Boys** | | | | | | | | | | | | |
| Communication | 1.23 | 3.60 | 1.10 – 1.38 | 1.05 | 0.81 | 0.93 – 1.19 | 1.21 | 3.13 | 1.07 – 1.36 | 1.04 | 0.63 | 0.92 – 1.19 |
| Gross motor | 1.28 | 4.10 | 1.14 – 1.43 | 0.92 | – 1.29 | 0.80 – 1.05 | 1.28 | 4.02 | 1.13 – 1.44 | 0.94 | – 0.84 | 0.82 – 1.08 |
| Fine motor | 1.09 | 1.88 | 1.00 – 1.20 | 0.98 | – 0.39 | 0.89 – 1.08 | 1.08 | 1.51 | 0.98 – 1.19 | 0.99 | – 0.12 | 0.89 – 1.10 |
| Problem-solving | 1.16 | 3.10 | 1.06 – 1.28 | 1.04 | 0.68 | 0.94 – 1.15 | 1.15 | 2.78 | 1.04 – 1.27 | 1.05 | 0.98 | 0.95 – 1.17 |
| Personal-social | 1.17 | 3.18 | 1.06 – 1.29 | 0.99 | – 0.21 | 0.89 – 1.10 | 1.16 | 2.99 | 1.05 – 1.28 | 1.01 | 0.14 | 0.90 – 1.12 |
| **Girls** | | | | | | | | | | | | |
| Communication | 1.33 | 3.43 | 1.13 – 1.56 | 0.98 | – 0.19 | 0.82 – 1.18 | 1.24 | 2.49 | 1.05 – 1.47 | 0.99 | –0.10 | 0.82 – 1.20 |
| Gross motor | 1.34 | 4.70 | 1.18 – 1.51 | 0.89 | – 1.59 | 0.77 – 1.03 | 1.29 | 3.94 | 1.14 – 1.46 | 0.88 | – 1.66 | 0.76 – 1.02 |
| Fine motor | 1.11 | 1.68 | 0.98–1.25 | 0.95 | – 0.75 | 0.83 – 1.09 | 1.10 | 1.48 | 0.97 – 1.25 | 0.90 | – 1.40 | 0.79 – 1.04 |
| Problem-solving | 1.24 | 3.57 | 1.10 – 1.39 | 0.98 | – 0.36 | 0.86 – 1.11 | 1.21 | 3.08 | 1.07 – 1.37 | 0.97 | – 0.44 | 0.85 – 1.11 |
| Personal-social | 1.38 | 4.34 | 1.19 – 1.60 | 1.03 | 0.38 | 0.87 – 1.22 | 1.29 | 3.22 | 1.10 – 1.50 | 1.02 | 0.25 | 0.86 – 1.22 |

[a]*n* = 62,308; excluding children born preterm, small-for-gestational-age, and those delivered by cesarean section.
Chest-to-head circumference ratio: low, <10th percentile; normal, 10th–90th percentile (reference group); high, >90th percentile of internally constructed growth chart.
aRR, adjusted risk ratio; cRR, crude risk ratio; 95%CI, 95% confidence interval.
Adjusted for parental age and educational status, maternal characteristics (geographic region at recruitment, parity, pre-pregnancy body mass index, iodine intake, and tobacco and alcohol use during pregnancy), as well as clinical conditions during pregnancy (hypertension, diabetes, Graves' disease, epilepsy, mental health conditions, psychological distress, infections during pregnancy, chorioamnionitis, and the use of steroids and psychotropic medications), along with gestational length.

**Table 4.** Bivariate association of anthropometric measurements with risk of developmental delay in the first 3 years for children

| | Low | | | High | | |
|---|---|---|---|---|---|---|
| | RR | *z* | 95%CI | RR | *z* | 95%CI |
| **Birthweight**[a] | | | | | | |
| **Boys** | | | | | | |
| Communication | 1.26 | 5.51 | 1.16 – 1.37 | 0.94 | – 1.03 | 0.84 – 1.06 |
| Gross motor | 1.29 | 5.72 | 1.18 – 1.41 | 1.02 | 0.32 | 0.91 – 1.14 |
| Fine motor | 1.24 | 6.25 | 1.16 – 1.33 | 0.93 | – 1.41 | 0.85 – 1.03 |
| Problem-solving | 1.25 | 6.36 | 1.17 – 1.34 | 0.99 | – 0.21 | 0.90 – 1.09 |
| Personal-social | 1.24 | 6.12 | 1.16 – 1.33 | 0.93 | – 1.41 | 0.85 – 1.03 |
| **Girls** | | | | | | |
| Communication | 1.42 | 5.73 | 1.26 – 1.60 | 0.97 | – 0.32 | 0.82 – 1.15 |
| Gross motor | 1.37 | 7.00 | 1.25 – 1.49 | 1.04 | 0.60 | 0.92 – 1.17 |
| Fine motor | 1.26 | 5.28 | 1.16 – 1.38 | 0.89 | – 1.82 | 0.79 – 1.01 |
| Problem-solving | 1.28 | 5.51 | 1.17 – 1.39 | 0.99 | – 0.14 | 0.88 – 1.12 |
| Personal-social | 1.40 | 6.12 | 1.26 – 1.57 | 0.96 | – 0.54 | 0.82 – 1.12 |
| **Chest circumference**[a] | | | | | | |
| **Boys** | | | | | | |
| Communication | 1.29 | 5.92 | 1.18 – 1.40 | 0.98 | – 0.43 | 0.87 – 1.09 |
| Gross motor | 1.39 | 7.50 | 1.28 – 1.52 | 1.05 | 0.78 | 0.93 – 1.18 |
| Fine motor | 1.22 | 5.73 | 1.14 – 1.31 | 0.91 | – 2.03 | 0.83 – 0.99 |
| Problem-solving | 1.26 | 6.40 | 1.17 – 1.35 | 0.97 | – 0.70 | 0.88 – 1.06 |
| Personal-social | 1.25 | 6.10 | 1.16 – 1.34 | 0.95 | – 1.05 | 0.87 – 1.04 |
| **Girls** | | | | | | |
| Communication | 1.38 | 5.18 | 1.22 – 1.56 | 0.92 | – 0.95 | 0.78 – 1.09 |
| Gross motor | 1.36 | 6.85 | 1.25 – 1.49 | 0.94 | – 1.04 | 0.83 – 1.06 |
| Fine motor | 1.22 | 4.42 | 1.12 – 1.33 | 0.94 | – 0.96 | 0.84 – 1.06 |
| Problem-solving | 1.26 | 5.11 | 1.15 – 1.37 | 0.94 | – 0.96 | 0.84 – 1.06 |
| Personal-social | 1.38 | 5.77 | 1.24 – 1.54 | 0.92 | – 1.10 | 0.79 – 1.07 |
| **Head circumference**[a] | | | | | | |
| **Boys** | | | | | | |
| Communication | 1.10 | 2.07 | 1.01 – 1.20 | 1.13 | 2.30 | 1.02 – 1.25 |
| Gross motor | 1.11 | 2.14 | 1.01 – 1.21 | 1.24 | 4.01 | 1.11 – 1.37 |
| Fine motor | 1.14 | 3.63 | 1.06 – 1.22 | 1.03 | 0.58 | 0.94 – 1.12 |
| Problem-solving | 1.09 | 2.19 | 1.01 – 1.17 | 1.08 | 1.75 | 0.99 – 1.18 |
| Personal-social | 1.14 | 3.44 | 1.06 – 1.22 | 1.06 | 1.33 | 0.97 – 1.16 |
| **Girls** | | | | | | |
| Communication | 1.24 | 3.24 | 1.09 – 1.42 | 1.03 | 0.34 | 0.88 – 1.20 |
| Gross motor | 1.11 | 2.11 | 1.01 – 1.22 | 1.27 | 4.39 | 1.14 – 1.41 |
| Fine motor | 1.17 | 3.25 | 1.06 – 1.28 | 1.03 | 0.49 | 0.92 – 1.14 |
| Problem-solving | 1.14 | 2.66 | 1.03 – 1.25 | 1.04 | 0.76 | 0.94 – 1.16 |
| Personal-social | 1.13 | 1.95 | 0.99 – 1.27 | 1.04 | 0.52 | 0.90 – 1.19 |

[a]Low, *z*-score<10th percentile; Normal, *z*-score 10–90th percentile (reference group); High, *z*-score>90th percentile.
RR, risk ratio; 95%CI, 95% confidence interval.

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**Table 5.** Area under the receiver operating characteristic curve (AUC) for predicting any developmental delay at 3 years of age by newborn measurements

| Measurement | Boys | Girls |
| --- | --- | --- |
| | 7805 cases (18.1%) | 3554 cases (8.7%) |
| Birthweight | 0.526 (0.519 – 0.533) | 0.528 (0.518 – 0.538) |
| Chest circumference | 0.526 (0.519 – 0.533) | 0.527 (0.517 – 0.537) |
| Head circumference | 0.513 (0.506 – 0.520) | 0.509 (0.499 – 0.519) |
| Chest-to-head circumference ratio | 0.520 (0.513 – 0.528) | 0.531 (0.521 – 0.541) |

Values represent AUC (95% confidence interval).

of handling unbalanced data. Moreover, we lacked objective measures, such as Doppler data, to evaluate the extent of intrauterine compromise among the chest-to-head circumference ratio groups. Participants excluded from this study had less favorable characteristics compared to those included, which may have biased the effect of a low chest-to-head circumference ratio on psychomotor development toward the null. Although the JECS population is relatively homogenous, minimizing the influence of ethnic disparity, further research is needed to determine the generalizability of our findings to other populations.

## Conclusions

Findings suggest that a low chest-to-head circumference ratio at birth is linked to an elevated risk of impaired neurodevelopment in children of both sexes. This association appears to be primarily driven by a relatively narrow chest rather than a large head. However, none of the anthropometric fetal growth indicators adequately predicted neurodevelopmental deficits at three years of age in children born without obvious congenital malformations.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S2040174424000412.

**Data availability statement.** Data are unsuitable for public deposition due to ethical restrictions and legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of 30 May 2003, amended on 9 September 2015) to publicly deposit the data containing personal information. Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, also restricts the open sharing of the epidemiologic data. All inquiries about access to data should be sent to: jecs-en@nies.go.jp. The person responsible for handling enquires sent to this e-mail address is Dr Shoji F. Nakayama, JECS Programme Office, National Institute for Environmental Studies.

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**Author contributions.** Naw Awn J-P: Conceptualization and design, data curation, analysis and interpretation of data, and drafting and revising the manuscript. Masamitsu Eitoku: Data curation, analysis and interpretation of data, and critical revision of the manuscript. Keiko Yamasaki: Data curation, analysis and interpretation of data, and critical revision of the manuscript. Naomi Mitsuda: Data curation, analysis and interpretation of data, and critical revision of the manuscript. Mikiya Fujieda: Analysis and interpretation of data, and critical revision of the manuscript. Nagamasa Maeda: Analysis and interpretation of data, and critical revision of the manuscript. Narufumi Suganuma: Funding acquisition, data curation, analysis and interpretation of data, and critical revision of the manuscript. JECS Group members: Data curation and critical revision of the manuscript. All authors have read and approved the final manuscript.

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**Competing interests.** None.

**Ethical standards.** The authors assert that all procedures contributing to this work comply with the ethical standards of the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (No.100910001) and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the ethics committees of all participating institutions. Written informed consent was obtained from all participants.

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