



Title	Influence of unbalanced large head on neurodevelopment in infancy : a longitudinal birth cohort study
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Citation	大阪大学, 2016, 博士論文
Version Type	VoR
URL	https://doi.org/10.18910/59651
rights	
Note	

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**Influence of unbalanced large head on neurodevelopment in infancy:
a longitudinal birth cohort study**

(出生時の不均衡に大きい頭部のサイズと子どもの神経発達との関連: 縦断的出生コホート研究)

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2016年6月 博士学位論文

ABSTRACT

Background:

Head circumference (HC) at birth has not been established as a predictor for subsequent neurodevelopmental impairments in the offspring. Relative measurement of head size, i.e., head size relative to body size, may be a useful index for neurodevelopmental disturbances.

Methods:

Participants comprised a consecutive series of mothers ($n = 707$) and their infants ($n = 743$) born between 24 December 2007 and 30 June 2011. The neurodevelopmental outcomes for the offspring were assessed by the Mullen Scales of Early Learning, consisting of gross motor (GM), fine motor (FM), visual reception (VR), receptive language (RL), and expressive language (EL), at 7 time-points from 1 month to 24 months of age. As a head size index (HSI), we applied the value of HC (cm) divided by body weight (BW, kg) for each of the infants. We also created a categorical variable for HSI, using the mean and 1 standard deviation for the HSI: infants with unbalanced large head (ULH) *v.* the comparison infants. For analysis, we employed multi-level mixed effects modelling.

Results:

The HSI negatively correlated with growth rates of neurodevelopment, particularly in GM and EL. The ULH infants had a significantly lower growth rate in all of the five domains, notably for EL ($p < .001$), compared with the comparison infants. However, linear growth patterns in the two groups revealed that at 1 month of age, the ULH group performed better in all of the five domains than the comparison group. Then, performance in the ULH group reversed in the subsequent course of the follow-up and, eventually, turned into delayed progress before 24 months of age.

Conclusions:

Both measures of HSI (continuous and categorical) predicted subsequent neurodevelopmental progress in infants. Our results suggest that HSI, in particular ULH, may be a useful measure to screen for infants with subsequent neurodevelopmental impairments.

Key words:

neurodevelopment, delayed growth, head size, birth cohort, unbalanced large head at birth

INTRODUCTION

Head circumference (HC) at birth reflects brain volume and brain development of the fetus in uterus.^{1,2} This is used to a major diagnostic and prognostic marker which is associated with various etiologies of neurodevelopmental disorders.^{3,4} Therefore, the measurement of HC at birth is performed as a part of the basic clinical assessment of the newborn. In particular, researchers have attended to the association between head growth attainment and neurodevelopment. However, several studies that investigated the relationship between HC at birth and neurodevelopmental outcomes in preterm-born children have failed to show positive results.⁵⁻¹¹ In these prior studies, researchers exclusively focused on preterm-born infants. However, failure in showing the association in a particular population does not necessarily eliminate the possibility that variation of HC is related to subsequent neurodevelopmental disturbances in the population as a whole. Therefore, it remains unanswered whether HC can serve as an index for impairments in neurodevelopmental progress.

Intriguingly, research on autism spectrum disorder (ASD), a neurodevelopmental condition, has indicated that babies with a large head size tend to have an increased risk of developing this condition. In fact, there are many studies reporting the association between ASD and large head size.¹²⁻¹⁷ However, the results are not entirely consistent; some studies have shown that individuals with ASD have a normal head size at birth,^{18,19} and others have failed to demonstrate the positive relationship between large head size and the risk of ASD.²⁰⁻²² Although, in a recent study of a systematic review and meta-analysis, Sacco et al.²³ have shown that there is an overall association between large head size and the risk of ASD, inconsistency across studies cannot be overlooked. In this regard, of note is a study by Grandgeorge et al.,²⁴ who investigated an association between the size of head relative to body size (i.e., body length) and the risk of ASD. They found that large head size relative to body length was more frequently observed among individuals later diagnosed with ASD than among those who developed normally. The finding suggests that relative measures rather than a direct one (HC itself) may be more powerful to predict subsequent impaired neurodevelopment.

Hence, we sought to investigate whether large head relative to body size at birth (i.e., birthweight) would be related to neurodevelopment in the offspring in a sample representative of the general population. We chose birthweight as a denominator rather than body length because the former is more accurate in measurement than the latter especially when measurements are conducted immediately after birth.²⁵ We tested the hypothesis that infants with unbalanced large head (ULH) would have delayed neurodevelopmental milestones during infancy compared with infants with a normal head size.

METHOD

This study was performed as a part of the Hamamatsu Birth Cohort Study for Mother and Children (HBC Study) which is an on-going project. Details of the HBC study have been described elsewhere.^{26,27}

Participants

Participants consisted of a consecutive series of mothers (n = 1065) and their infants (n = 1152) born between 24 December 2007 and 30 June 2011; some offspring (n = 173) were born from the same mother during the recruitment period and, thus, the number of the infants were larger than that of the mothers. All women who visited in the first or second trimester of pregnancy at either of our two research sites, the Hamamatsu University Hospital and Kato Maternity Clinic, were invited to participate in the study. In Japan, pregnant women can freely choose any maternity clinic, from a private clinic to a large general hospital. There was no between-site difference in demographic characteristics of the participants included in the analyses; the only one exception to this was age of mothers. Mothers who visited Kato Maternity Clinic first were younger than those who visited the Hamamatsu University Hospital first. All of the mothers who agreed to participate in the study, including those from Kato Maternity Clinic, gave birth at the same facility, i.e., Hamamatsu University Hospital. The assessment after birth was also performed at the same facility (Hamamatsu University Hospital). By referring to the reports from the Department of Health, Labour and Welfare, Japan,²⁸ and to the statistical data from 2012 Employment Status Survey, Japan,²⁹ we found that the enrolled parturients in this study were representative of Japanese parturients with respect to age, socioeconomic status and parity, and their offspring were representative of Japanese newborn populations with respect to birthweight and gestational age at birth. Therefore, participants in this cohort are considered to be a fairly representative sample of the general population.^{26,27}

We excluded 160 participating mothers and 167 infants who missed 6 or more of the total 7 follow-up evaluations after birth (Fig. 1). The major reason for loss to follow-up was a Japanese traditional support system for childbirth, called “satogaeri bunben”, which has been described in detail in our previous study.³⁰ We also excluded two mother-infant dyads as the infants were diagnosed with Down syndrome. Finally, we further excluded 196 mothers and their 240 infants who missed measurement of HC at birth. Thus, 743 infants (64.5%) and 707 mothers (66.4%) were eventually included in the analyses.

Measurements

Outcome: developmental assessment

Evaluation of neurodevelopment progress was made using the Mullen Scales of Early Learning (MSEL). The MSEL is a composite scale for assessing child neurodevelopment and composed five subscales: gross motor (GM), fine motor (FM), visual reception (VR), receptive language (RL), and expressive language (EL). We performed the measurements when the infants reached the ages of 1, 4, 6, 10, 14, 18, and 24 months.

Prior to follow-up assessments of the birth cohort, two experienced clinicians performed 3-month video training sessions, through which agreement of their scoring of each item on the MSEL scale was attained. Subsequently, separate 3-month video training sessions were set up, including additional 5 assessors (child health professionals), who engaged in actual ascertainment. Because the assessment criteria change according to the development (i.e., ageing), similar training and quality-maintaining sessions using video recorded assessments were repeated prior to each of the 7 time-point follow-ups. Developmental assessments with MSEL were executed without referring to previously evaluated data. Information about demographic variables, which was collected by

independent and separate researchers, was kept blind to the assessors for the neurodevelopment.

We employed the Japanese version of MSEL T-scores which were created using our HBC sample.³¹ MSEL T-scores represent standardised measurement at any developing age (i.e., mean of 50 and standard deviation, SD, of 10), and are a commonly used index which enables one to easily discern deviations from the normative development.

Predictor: standardised head size index (sHSI), categorical head size index (cHSI), and unbalanced large head (ULH) group

Head circumference (HC) was measured by attending obstetricians or midwives, based on occipital-frontal circumference measures at birth. As an index of unbalanced head size, we used the value of HC (cm) divided by body weight (BW, kg) for each of the offspring. In the analyses, we considered this as both continuous and categorical. The raw HC/BW values was standardised by applying 0-centring and dividing it by its standard deviation (SD); the obtained new variable was designated as standardised HSI (sHSI) hereafter. This was made to ease interpretations of the relationship between the predictor (HSI) and outcome measurements; for instance, an estimated coefficient would correspond to a change in the T-score in a certain domain of MSEL for every one unit (i.e., 1 SD) change in the predictor (sHSI). In addition, we dichotomised sHSI, using the cutoff point of 1 (corresponding to mean+1 SD, as sHSI has a mean of 0 due to zero-centering), into categorical head size index (cHSI). With this variable, we defined unbalanced large head (ULH) group as of cHSI above cutoff (i.e. $sHSI > 1$) and the comparison group as of cHSI equals to or below cutoff ($sHSI \leq 1$).

Background assessment and covariates

As covariates that may affect neurodevelopmental progress in the offspring, we included the following variables: gender, gestational age, birth height, low birthweight (LBW: less than 2,500 g), and small for gestational age (SGA: weight below the 10th percentile for gestational age) for infants; age,

education, smoking during pregnancy, and a history of mental problems for mothers; age and education for fathers; and parental income. Data on the demographic characteristics of mothers and fathers were collected from mothers during pregnancy.

Statistical Analysis

The multi-level mixed-effects model was employed to allow for family clustering (i.e., siblings from the same mother) and correlations between the repeated nature of outcome measures (7 time-points measurement) (MSEL) within each individual infant. To effectively use all data available for computation, we opted for random intercept and random slope modelling.

We first examined the relationship between sHSI (continuous) and each of the 5 MSEL domains over the follow-up period (i.e, from 1 month to 24 months of age), properly taking covariates into account. Then, we went on examining whether the ULH infants would have a distinctive pattern of growth compared with the comparison group, using the categorised measure of HSI (cHSI). In the procedures, we focused on the presence of a significant group x slope interaction effect in the model. If significant interactions were detected, this would indicate that two groups have a different pattern of growth in the neurodevelopment. $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed with Stata version 13.1.

Ethical Issues

The study protocol was approved by the Hamamatsu University School of Medicine and University Hospital Ethics Committee. Written informed consent was obtained from each mother for her own and her infant participation.

RESULTS

Characteristics of infants and their parents

The study sample comprised 743 infants. As shown in Table 1, the proportion of male infants was 49.3%. The average gestational age was 39.0 weeks (SD 1.5), birthweight 2953.6 g (SD 440.7), birth height 49.5 cm (SD 2.5), and HC 33.1 cm (SD 1.4). The mean maternal and paternal age was 31.4 years (SD 5.0) and 33.3 years (SD 5.9), respectively. The mean annual parental income was 5.99 million JPY (SD 3.22). These figures are considered to be fairly representative of the general population in reference to national maternity reports²⁸ and statistics of employment status survey in Japan.²⁹ The mean value of HSI before standardisation was 11.5 (SD 1.8).

Relationship between standardised head size index (sHSI) at birth and subsequent growth rates of neurodevelopment

Multi-level mixed-effects models analysis revealed a significant time (month) x sHSI interaction for GM ($p=.02$) and EL ($p<.01$), as shown in Table 2 (crude model). The coefficient for GM indicates that infants with one unit of sHSI (i.e, 1 SD) at birth had a 1.15 lower T-score on GM (0.05×23 mths) at 24 months of age, relative to infants with sHSI equal to 0 (i.e., normative head size). Similarly, the coefficient for EL indicates that infants with one unit of sHSI at birth had a 1.38 lower EL score (0.06×23 mths) at 24 months of age, compared with infants with a normative head size. These coefficients and the significant level virtually remained unchanged, after adjustment for covariates; in this analysis of the continuous measure, all covariates considered a priori were controlled for. There was no relationship between sHSI and growth rate during infancy in the other three domains (Table 2).

Two group comparison of neurodevelopmental growth rates: infants with unbalanced large head (ULH) vs comparison infants

The ULH group consisted of 75 (10.1 %) infants, and the remaining (n=668) were the comparison group. As shown in Table 1, the mean values for the following variables were all lower in the ULH group than in the comparison group: gestational age, birthweight, birth height, and HC at birth. The frequency of LBW and SGA was higher in the ULH infants than in the comparison group. Mothers of the ULH infants more often had a history of mental problems than mothers of the comparison group. These variables found to significantly differ between the two groups were taken into account in the subsequent analyses.

Multi-level mixed-effects models showed a significant time x group interaction in all of the five domains, notably for EL ($p = .001$), in the crude analyses (left column in Table 3). These results with negative coefficients indicate that there was a significantly lower rate of growth over the follow-up period in the ULH group than in the comparison group. These significant interactions remained unchanged even when covariates were controlled for; in fact, coefficients estimated were precisely the same except for a minimal change in EL, -0.24 to -0.23, after covariates were fully adjusted for.

Table 3 also shows that there was, in the fully adjusted model, a significant group grand-mean difference in the score of GM ($p = .01$), VR ($p = .04$), and EL ($p < .001$) at 1 month, indicating that ULH infants performed better in these domains early in life (i.e., at one month of age) than the comparison infants. For example, the T-score of EL was estimated to be markedly higher by 4.47 in the ULH group at 1 month of age than in the comparison group in the full model.

Figure 2, which was derived from the full adjustment model, visualises the differences in the growth rate between the two groups. While, as expected, there was no substantive pattern of growth in the comparison group (almost flat in the slopes around the average of the T-scores, roughly 48), over the follow-up period, there was a marked downward slope for the ULH group. At the early stage (i.e., at 1 month of age), the ULH group performed better in all of the five domains of MSEL than the comparison group, although 95% CIs of the estimates overlap in some domains (FM, RL), indicating

non-significance differences. As infants grow older, the group differences in the T-score diminish, the two slopes cross each other and, after the crossing, the ULH infants become poorer in neurodevelopmental performance than the comparison group. The inverse time point takes place around 20 months of age for the three domains (GM, VR, and EL), at 16 months of age for FM, and at 12 months of age for RL.

Attrition

Attrition is an important concern in this type of longitudinal studies. If particular patterns of missingness had taken place in the measurement of HC in infants, this would have biased the results. However, whether infants provided information on HC at birth or not did not correlate with subsequent growth rates of the performance on MSEL (time x group (HC missing vs HC provided) interaction: $p < .11$). Thus, missingness of HC is unlikely to have affected the findings of the present study. Although 91% of the initially enrolled mother-infant dyads, after eliminating "satogaeri bunben", were retained in the analysis, not all infants participated in each of the total 7 assessment sessions (from 1 month to 24 months of age). If characteristics in infants varied according to the number of assessments (for example, more problematic infants tended not to turn up for planned evaluations), this may have distorted the statistical estimation procedures in the present study. However, it was found that frequencies of evaluations were not associated with performance on MSEL in our sample (Nishimura et al.,³¹ 2016) and, thus, variation of the frequency of assessment visits is unlikely to have affected the results.

DISCUSSION

We found that the head size index (HSI, continuous measure) negatively correlated with growth rates of neurodevelopment, particularly in gross motor (GM) and expressive language (EL), as evaluated with Mullen Scales of Early Learning (MSEL), during 1 to 24 months of age. Further, we also detected that infants with unbalanced large head (ULH) had a significantly lower growth rate in all of the five domains examined, notably for EL, compared with the comparison group of infants. Inspection of the regression lines for the two groups showed that the ULH group had the higher T-scores in all of the five domains than the comparison group at one month of age, but performance in the ULH group reversed over the follow-up period, indicating that privileged growth patterns in ULH infants observed early in life disappear and eventually turn into delayed progress.

In a population-based study, Wright et al.³² reported no relationship between the extremes of head size (HC <-2 SDs or >2 SDs from the mean), and later neurodevelopmental problems. Similarly, another population-based birth cohort study by Álamo-Junquera et al.³³ has concluded that HC at birth is not associated with neurodevelopmental progress. Thus, these recently conducted population-based studies failed to demonstrate that HC can serve as a predictor for subsequent neurodevelopment impairments. However, we found in this study of a birth cohort, representative of the general population, that the HSI, a measure of HC relative to body size, negatively correlated with growth rates of neurodevelopment, particularly in domains of GM and EL. Together, these results suggest that the HSI at birth instead of HC itself can be used to screen for infants with impaired neurodevelopmental milestones.

Surprisingly, we found the infants with ULH to be at an advantage in terms of neurodevelopmental performance early in life (i.e., at 1 month of age). However, such advantage faded out and,

conversely, ULH infants became underprivileged in the subsequent developments towards the end of the follow-up. Of interest in this context is a prospective study reporting that children with autism spectrum disorder (ASD) display normal developmental progress at 6 months of age, but shift into poor performance in neurodevelopment by 14 months of age.³⁴ This finding, together with ours, indicates that ULH infants may have characteristics in common with infants with ASD. However, only a part of our ULH infants will be identified as having a diagnosis of ASD when diagnostic evaluations are carried out in the subsequent follow-ups since the prevalence of ASD should be substantially lower than that of our ULH group (10.1%) in the cohort.

One may raise a question as to whether an overall delayed growth of neurodevelopment in the ULH group may be accounted for by innate growth retardation in this population. Arcangeli et al.³⁵ have reported in a systematic review that small fetuses born at term with or without growth restriction have lower neurodevelopmental scores than a normal control group. There was a significantly higher proportion of small for gestational age (SGA) in the ULH group in this study than in the comparison group. However, our finding of impaired neurodevelopment in the ULH group cannot be attributed to SGA infants as the interaction of group x slope (regression line) remained significant after covariates, including SGA, were adjusted for.

As aforementioned, our sample of infants with ULH, at least a proportion of them, may share features similar to ASD which is characterised as mainly having language deficits. In effect, infants with ULH also showed delayed growth in language functioning in both RL and EL. However, the patterns of occurrence of delayed growth in neurodevelopment in our ULH infants are rather complex. The point at which infants with ULH made the transition to downward progress varied according to domains of the functions; in order of time occurrence, RL (around 12 months of age), FM (around 16 months of age), and GM, VR, and EL (around 20 months of age). Such varying emergences (i.e., extended and variable occurrences) are in marked contrast with patterns reported for ASD. For instance, a

study of developmental trajectories of ASD by Landa et al.,³⁶ employing the MSEL, has shown that developmental delays in ASD become manifest in the four domains of MSEL (except for VR) by 14 months of age. Therefore, our findings suggest that infants with ULH may be composed of conflation of various types of broadly defined neurodevelopmental disorders that possibly include specific language disorder, and developmental coordination disorder, along with ASD. Additional follow-up studies are needed for establishing diagnoses among infants with ULH.

Although we used both continuous (standardised HSI, sHSI) and categorical (cHSI) indices for evaluating the consequences of the disproportionate head size, the latter was arbitrary; we dichotomised infants into two groups (ULH infants vs the remaining infants) using a cutoff of mean+1 SD for HSI. To secure such arbitrariness, we conducted further analysis using a more restricted cutoff of 90th centile. The results remained largely unchanged, although the effect of the group x slope interaction became at a marginally significant level in two domains (p =.09 for FM; p =.07 for VR), after covariates were fully adjusted for (see Table 1S, Supplement).

Strengths and limitations

The strength of this study is that our sample comprised a representative sample of infants in the general population. In analyses, we opted for a multi-level mixed-effects modelling technique which allows for optimal use of all available data. If we, instead, used fixed effects approaches on which listwise deletion is often used, this could have biased the results towards the null hypothesis due to loss of statistical power. As one of the limitations of this study, it is uncertain whether infants with missing data were allocated to each of 2 groups (i.e., ULH group vs the remaining group) with equal probabilities. Another limitation is that the developmental slopes we examined were limited to the first two years of life, and it is possible that these patterns may change after further follow-ups. Although infants with "satogaeri bunben" who were eliminated from the analyses were identical to infants who participated in the study in terms of performance on MSEL, some of background

characteristics in their parents differed between the two groups; parents of infants with "satogaeri bunben" were younger than parents who participated in the study. There is a possibility that infants with poor neurodevelopmental progress born to relatively young parents may have been eliminated from the analyses. In the future, prospective birth cohorts with longer follow-ups are needed to substantiate present findings at later ages. Furthermore, it is necessary to verify whether the HSI is a useful tool for screening for neurodevelopmental disorders and other specific problems.

Funding

This work was supported by the Strategic Research Programme for Brain Sciences (“Integrated research on neuropsychiatric disorders”) (KJT and NM) and Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science & Technology in Japan (RO: 26463432, KJT: 25461758, NT: 26670540, 24659542).

Acknowledgements

The authors would like to thank Dr. Tetsuo Kato of the Kato Maternity Clinic for promoting recruitment of potential participants. The authors are also grateful to Drs. N. Kanayama, H. Itoh, K. Sugihara, M. Sugimura, K. Takeuchi, K. Suzuki, Y. Murakami, Y. Koumura, Y. Miyabe, K. Hirai, Y. Nakamura, R. Koizumi, H. Murakami, Y. Kobayashi-Koumura, and K. Muramatsu-Kato, and all the attending obstetricians. The authors also thank Ms. Kiyomi Hinoki, and all the midwives and staff at the maternity clinic of the Hamamatsu University School of Medicine, for enrolling participants.

The HBC study team includes Ms. Y. Kugizaki, C. Nakayasu, A. Okumura, Y. Suzuki, N. Kodera, E. Higashimoto, A. Nakamura, R. Takabayashi, T. Mori, H. Muraki, M. Narumiya, M. Honda, Y. Seno, E. Sato, C. Nishizawa, Mr. R. Nakahara, Drs. T. Harada, T. Nishimura, M. Wakuta, K. Suzuki, Y. Kameno, T. Wakuda, D. Kurita, K. Takebayashi, Y. Iwata, S. Takagai, T. Sugiyama, M. Tsujii, A.A. Pillai, T. Ismail, K. Matsumoto, K. Iwata, C. Shimmura, Y. Yoshihara, S. Yamamoto, M. Kawai, K. Nakamura, H. Matsuzaki, G. Sugihara, K. Hirano, Y. Endoh, and T. Suzuki. Finally, we thank all the participating families and infants.

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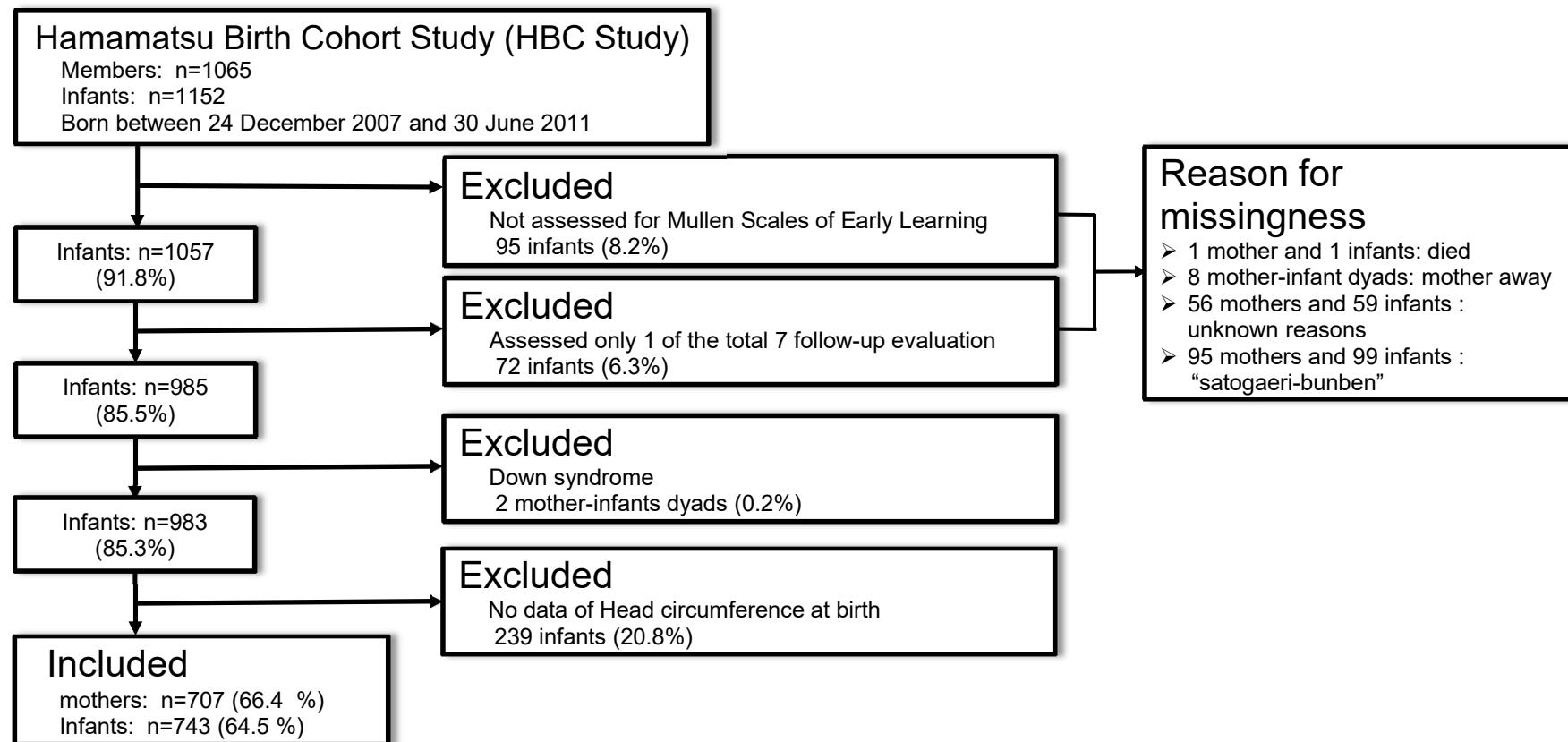


Figure 1 Flow chart of participants who met inclusion / exclusion criteria

Table 1 Characteristics of participating infants and their parents.

	Total n = 743 (100%)	cHSI group			p value
		ULH group n = 75 (10.1%)	Comparison group n = 668 (89.9%)		
Gender					
Male	n (%)	366 (49.3)	31 (41.3)	346 (48.2)	0.09
Female		377 (50.7)	44 (58.7)	322 (51.8)	
Gestational age [weeks]	Mean (SD)	39.0 (1.5)	36.7 (2.3)	39.2 (1.2)	< 0.0001
Birthweight [g]	Mean (SD)	2953.6 (440.7)	2128.4 (346.1)	3046.2 (342.9)	< 0.0001
Small for Gestational Age					
< 10th percentile	n (%)	78 (10.5)	40 (53.3)	38 (5.7)	< 0.001
10th - 100th percentile		665 (89.5)	35 (46.7)	630 (94.3)	
Low birthweight					
Low birthweight (< 2,500g)	n (%)	94 (12.7)	72 (96.0)	22 (3.3)	< 0.001
Normal birthweight		649 (87.3)	3 (4.0)	646 (96.7)	
Birth height [cm]	Mean (SD)	49.5 (2.5)	44.8 (3.6)	50.0 (1.7)	< 0.0001
Head Circumference at birth [cm]	Mean (SD)	33.1 (1.4)	31.7 (1.6)	33.3 (1.3)	< 0.0001
Maternal age at birth [years]	Mean (SD)	31.4 (5.0)	31.7 (5.3)	31.4 (5.0)	0.58
Maternal education at birth					
<12 years	n (%)	43 (5.8)	5 (6.7)	38 (5.7)	0.86
12-15 years		525 (70.7)	54 (72.0)	471 (70.5)	
≥ 16years		175 (23.6)	16 (21.3)	159 (23.8)	
Maternal smoking during pregnancy					
smoking	n (%)	63 (8.5)	9 (12.0)	54 (8.0)	0.25
non smoking		680 (91.5)	66 (88.0)	614 (91.9)	
a history of mental problem in mother					
Yes	n (%)	108 (14.5)	18 (24.0)	90 (13.5)	0.014
No		635 (85.5)	57 (76.0)	578 (86.5)	
Paternal age at birth [years]	Mean (SD)	33.3 (5.9)	33.4 (5.8)	33.3 (6.0)	0.88
Paternal education at birth					
<12 years	n (%)	62 (8.3)	8 (10.7)	54 (8.1)	0.65
12-15 years		396 (53.3)	37 (49.3)	359 (53.7)	
≥ 16years		285 (38.4)	30 (40.0)	255 (38.1)	
Parental income at 2nd trimester of the index pregnancy [million JPY]	Mean (SD)	5.99 (3.22)	6.02 (3.43)	5.99 (3.20)	0.94
Head circumference at birth [cm] / birthweight [kg]		11.5 (1.8)			

cHSI: categorical head size index, ULH: unbalanced large head

Table 2 Neurodevelopmental progress predicted by infant's sHSI value

Domain		Crude model			Full adjustment model			p value
		Coefficient*	95%CI	p value	Coefficient*	95%CI	p value	
Gross Motor	sHSI	0.001	-0.53 0.53	1.00	-0.70	-1.65 0.25	0.15	
	time (month)	-0.03	-0.07 0.01	0.09	-0.03	-0.07 0.00	0.09	
	time (month) × sHSI	-0.05	-0.08 -0.01	0.02	-0.05	-0.09 -0.01	0.02	
Fine Motor	sHSI	0.01	-0.49 0.51	0.98	0.32	-0.52 1.15	0.46	
	time (month)	-0.06	-0.10 -0.03	0.001	-0.07	-0.10 -0.03	<0.001	
	time (month) × sHSI	-0.03	-0.07 0.00	0.08	-0.03	-0.07 0.00	0.08	
Visual Reception	sHSI	-0.13	-0.66 0.39	0.62	0.52	-0.36 1.40	0.24	
	time (month)	0.02	-0.02 0.06	0.23	0.02	-0.02 0.06	0.26	
	time (month) × sHSI	-0.03	-0.07 0.01	0.21	-0.03	-0.07 0.01	0.20	
Receptive Language	sHSI	-0.28	-0.79 0.23	0.28	-0.34	-1.26 0.52	0.44	
	time (month)	0.04	0.00 0.08	0.03	0.04	0.00 0.08	0.04	
	time (month) × sHSI	-0.03	-0.07 0.01	0.18	-0.03	-0.07 0.01	0.17	
Expressive Language	sHSI	-0.12	-0.61 0.36	0.62	-0.42	-1.26 0.33	0.33	
	time (month)	-0.05	-0.09 -0.01	0.02	-0.05	-0.09 -0.01	0.02	
	time (month) × sHSI	-0.06	-0.10 -0.01	<0.01	-0.06	-0.10 -0.02	<0.01	

sHSI: standardised head size index, CI: confidence interval

*: coefficients were produced to take the variable of month (time) as starting at one month of age, rather than at birth.

Full adjustment model: adjusted for gender, gestational age, birth height, small for gestational age, low birthweight, maternal age and education, maternal smoking during pregnancy, a history of mental problems in mother, paternal age and education, and parental income.

Table 3 Neurodevelopmental progress predicted by cHSI (the ULH group vs the comparison group)

Domain	Crude model			Partial Adjustment model			Full adjustment model			
	Coefficient*	95%CI	p value	Coefficient*	95%CI	p value	Coefficient*	95%CI	p value	
Gross Motor	cHSI	2.60	0.88 4.33	<0.01	3.74	0.91 6.58	0.01	3.56	0.73 6.38	0.01
	time (month)	-0.01	-0.05 0.03	0.49	-0.01	-0.05 0.02	0.48	-0.01	-0.05 0.02	0.47
	time (month) x cHSI	-0.18	-0.30 -0.05	<0.01	-0.18	-0.30 -0.05	<0.01	-0.18	-0.30 -0.05	<0.01
Fine Motor	cHSI	1.23	-0.39 2.85	0.14	2.14	-0.37 4.65	0.10	1.97	-0.52 4.50	0.12
	time (month)	-0.05	-0.09 -0.01	0.01	-0.05	-0.09 -0.01	<0.01	-0.05	-0.09 -0.01	<0.01
	time (month) x cHSI	-0.13	-0.25 -0.01	0.04	-0.13	-0.25 0.00	0.04	-0.13	-0.25 0.00	0.04
Visual Reception	cHSI	0.70	-1.01 2.41	0.42	2.95	0.32 5.57	0.03	2.75	0.12 5.37	0.04
	time (month)	0.04	0.00 0.08	0.07	0.04	0.00 0.08	0.08	0.37	0.00 0.08	0.08
	time (month) x cHSI	-0.14	-0.27 -0.01	0.04	-0.14	-0.27 -0.01	0.04	-0.14	-0.27 -0.01	0.04
Receptive Language	cHSI	0.47	-1.18 2.13	0.58	1.81	-0.78 4.39	0.17	1.93	-0.65 4.51	0.14
	time (month)	0.06	0.02 0.10	<0.01	0.06	0.02 0.10	<0.01	0.06	0.14 0.98	<0.01
	time (month) x cHSI	-0.15	-0.28 -0.01	0.03	-0.15	-0.28 -0.01	0.03	-0.15	-0.28 -0.01	0.03
Expressive Language	cHSI	2.29	0.72 3.87	<0.01	4.41	1.91 6.91	0.001	4.47	1.98 6.87	<0.001
	time (month)	-0.03	-0.07 0.02	0.24	-0.03	-0.07 0.02	0.23	-0.03	-0.07 0.02	0.16
	time (month) x cHSI	-0.24	-0.37 -0.10	0.001	-0.23	-0.37 -0.10	0.001	-0.23	-0.37 -0.10	0.001

cHSI: categorised head size index, ULH: unbalanced large head, CI: confidence interval

*: coefficients were produced to take the variable of month (time) as starting at one month of age, rather than at birth.

Partial adjustment model: adjusted for gestational age, birth height, small for gestational age, low birthweight, a history of mental problems in mother.

Fully adjustment model: adjusted for all covariates in partial adjustment model plus gender, maternal age and education, maternal smoking during pregnancy, paternal age and education, and parental income.

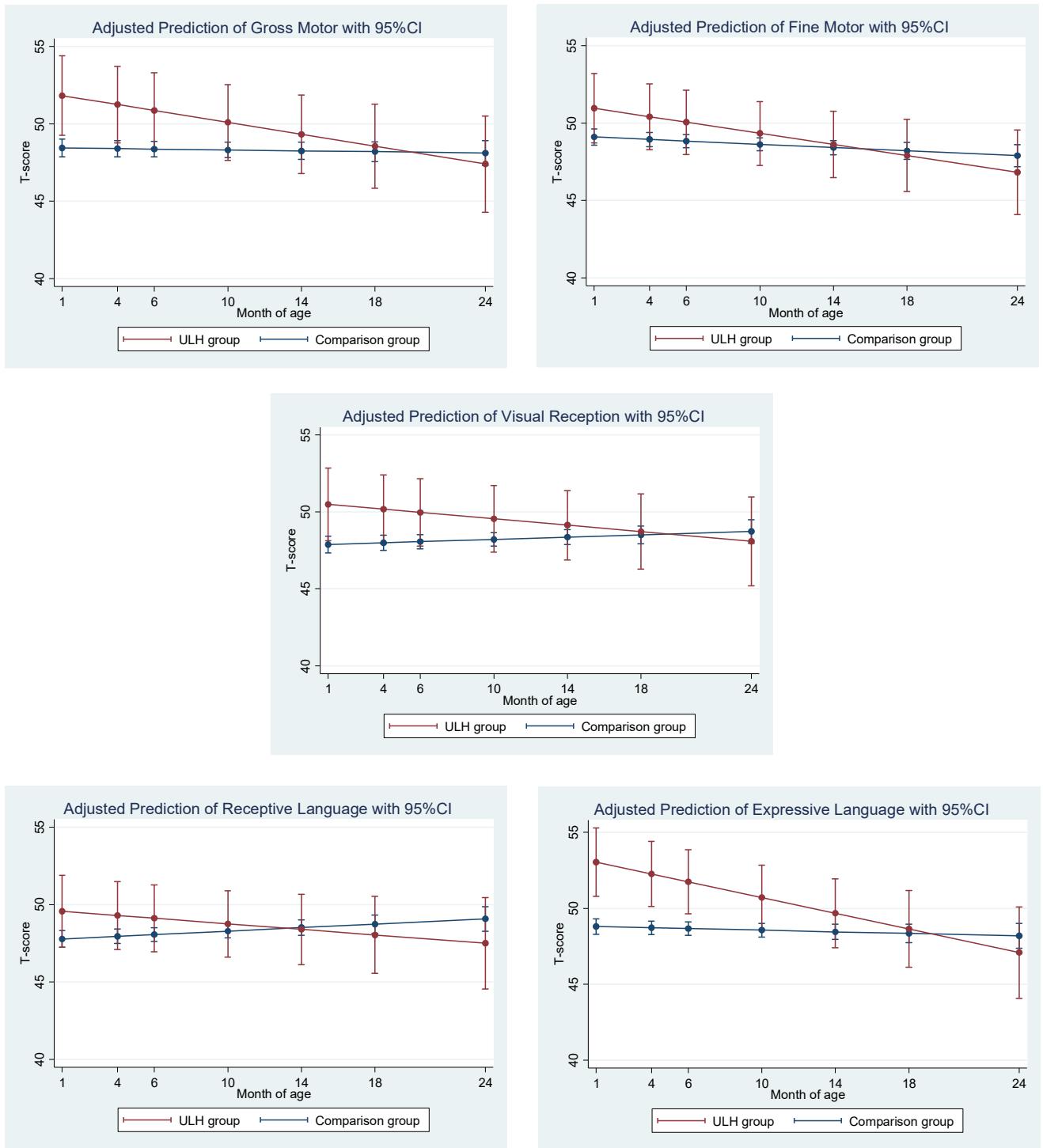


Figure 2 Neurodevelopmental progress predicted by cHSI (the ULH group vs the comparison group). The fully adjusted model was used: adjusted for gender, gestational age, birth height, small for gestational age, low birthweight, maternal age and education, maternal smoking during pregnancy, a history of mental problems in mothers, paternal age and education, and parental income. CI: confidence interval, ULH: unbaranced large head, cHSI: categorical head size index

Table 1S Neurodevelopmental progress predicted by infant's head size in the two groups: ULH (greater than 90%) groups vs comparison group (less than or equal to 90%)

Domain	Full adjustment model				
	Coefficient*	95%CI		p value	
Gross Motor	cHSI	3.78	0.89	6.67	0.01
	time (month)	-0.02	-0.05	0.02	0.44
	time (month) x cHSI	-0.17	-0.30	-0.04	0.01
Fine Motor	cHSI	1.88	-0.66	4.43	0.15
	time (month)	-0.05	-0.09	-0.02	0.01
	time (month) x cHSI	-0.11	-0.23	0.02	0.09
Visual Reception	cHSI	3.31	0.62	5.99	0.02
	time (month)	0.03	-0.01	0.08	0.10
	time (month) x cHSI	-0.12	-0.26	0.01	0.07
Receptive Language	cHSI	2.15	-0.48	4.79	0.11
	time (month)	0.06	0.01	0.10	0.01
	time (month) x cHSI	-0.15	-0.28	-0.01	0.04
Expressive Language	cHSI	4.70	2.15	7.24	<0.001
	time (month)	-0.03	-0.07	0.01	0.20
	time (month) x cHSI	-0.22	-0.36	-0.09	<0.001

ULH: unbalanced large head, cHSI: categorised head size index, CI: confidence interval

*: the coefficients were produced as if time scale started at 1 month of age, not at birth.

Full adjustment model: adjusted for gender, gestational age, birth height, small for gestational age, low birthweight, maternal age and education, maternal smoking during pregnancy, a history of mental problems in mothers, paternal age and education, and parental income.