

SUPPLEMENTARY MATERIAL

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

Table S1. ASQ-3 cutoff scores (<2 SD from the mean) by age and study.

Age, months	Domain	Original ASQ-3 ^a	J-ASQ-3 ^b	Current study
6	Communication	29.65	22.93	29.06
6	Gross motor	22.25	15.12	8.49
6	Fine motor	25.14	16.24	13.43
6	Problem solving	27.72	26.27	19.79
6	Personal-social	25.34	7.88	4.83
12	Communication	15.64	4.53	11.44
12	Gross motor	21.49	9.43	9.15
12	Fine motor	34.50	25.47	25.99
12	Problem solving	27.32	15.37	16.08
12	Personal-social	21.73	4.95	8.67
18	Communication	13.06	5.82	6.96
18	Gross motor	37.38	37.59	36.80
18	Fine motor	34.32	26.76	29.29
18	Problem solving	25.74	15.93	18.11
18	Personal-social	27.19	24.57	28.40
24	Communication	25.17	14.33	14.43
24	Gross motor	38.07	39.13	36.59
24	Fine motor	35.16	33.48	35.53
24	Problem solving	29.78	29.38	28.13
24	Personal-social	31.54	25.22	30.35
30	Communication	33.30	26.01	30.69
30	Gross motor	36.14	38.36	39.09
30	Fine motor	19.25	21.03	22.79
30	Problem solving	27.08	25.78	27.81
30	Personal-social	32.01	29.70	30.66
36	Communication	30.99	29.95	32.78
36	Gross motor	36.99	39.26	39.77
36	Fine motor	18.07	27.91	24.40
36	Problem solving	30.29	30.03	30.84
36	Personal-social	35.33	29.89	30.90

^a Ages and Stages Questionnaires, third edition. (Squires J, Twombly E, Bricker D, Potter L. ASQ-3 User's Guide. Brookes Publishing, Baltimore, 2009.)

^b Japanese version of the Ages and Stages Questionnaires, third edition. (Mezawa H, Aoki S, Nakayama SF, et al. Psychometric profile of the Ages and Stages Questionnaires, Japanese translation. *Pediatr Int.* 2019; 61, 1086-1095.)

Table S2. Percentage of children with missing information for each developmental domain in relation to age at assessment.

Developmental domain	Age at assessment (months)					
	6	12	18	24	30	36
	%					
Communication	8.3	10.9	15.6	12.3	14.4	12.5
Gross motor	8.3	10.9	15.5	12.3	14.4	12.4
Fine motor	8.5	10.9	15.6	12.3	14.8	12.7
Problem solving	8.3	11.0	16.0	12.5	14.6	13.2
Personal-social	8.4	11.1	15.6	12.4	14.5	12.6

Table S3. Characteristics of the population according to inclusion status.

Characteristics	Included	Excluded	<i>p</i> value ^a
	(n = 84,311)	(n = 13,728)	
	Mean (SD) or number (%)		
Maternal information			
Geographic regions at recruitment ^b			0.123
Group 1	21,701 (25.7)	3622 (26.4)	
Group 2	51,411 (61.0)	8245 (60.1)	
Group 3	11,199 (13.3)	1861 (13.6)	
Age, y	31.3 (5.0)	30.1 (5.5)	<0.001
Age category			<0.001
≤24 y	7564 (9.0)	2295 (16.7)	
25–34 y	53,524 (63.5)	8273 (60.3)	
≥35 y	23,220 (27.5)	3152 (23.0)	
Missing	3 (0.0)	8 (0.1)	
Pre-pregnancy BMI			<0.001
<18.5 kg/m ²	13,608 (16.1)	2248 (16.4)	
18.5–24.9 kg/m ²	62,067 (73.6)	9492 (69.1)	
≥25 kg/m ²	8594 (10.2)	1901 (13.9)	
Missing	42 (0.1)	87 (0.6)	
Education			<0.001
High school or less	29,220 (34.7)	5579 (40.6)	
Vocational school/College	35,549 (42.2)	4713 (34.3)	
University or higher	18,618 (22.1)	2116 (15.4)	
Missing	924 (1.1)	1320 (9.6)	
Tobacco use during pregnancy			<0.001
Never	49,577 (58.8)	6353 (46.3)	
Former	30,270 (35.9)	5222 (38.0)	
Current	3450 (4.1)	1190 (8.7)	
Missing	1014 (1.2)	963 (7.0)	
Alcohol consumption during pregnancy			<0.001
Never	29,025 (34.4)	4342 (31.6)	
Former	46,059 (54.6)	7348 (53.5)	
Current	8428 (10.0)	1132 (8.3)	
Missing	799 (1.0)	906 (6.6)	
Iodine intake during pregnancy, µg/day			<0.001
1st tertile	27,638 (32.8)	4740 (34.5)	

2nd tertile	28,014 (33.2)	3913 (28.5)	
3rd tertile	28,150 (33.4)	3885 (28.3)	
Missing	509 (0.6)	1190 (8.7)	
Maternal clinical information during pregnancy			
Hypertension ^c (yes)	2779 (3.3)	685 (5.0)	<0.001
Missing	0	288 (2.1)	
Diabetes ^d (yes)	2601 (3.1)	453 (3.3)	<0.001
Missing	0	288 (2.1)	
Graves' disease (yes)	557 (0.7)	80 (0.6)	<0.001
Missing	0	288 (2.1)	
Epilepsy (yes)	204 (0.2)	43 (0.3)	<0.001
Missing	0	288 (2.1)	
Mental health conditions ^e (yes)	639 (0.8)	133 (1.0)	<0.001
Missing	0	288 (2.1)	
Psychological distress ^f (yes)	24,139 (28.6)	5563 (40.5)	<0.001
TORCH infection ^g (yes)	1927 (2.3)	384 (2.8)	<0.001
Missing	56,848 (67.4)	9459 (68.9)	
Intrauterine infection (yes)	453 (0.5)	121 (0.9)	<0.001
Missing	0	288 (2.1)	
Steroid use (yes)	2209 (2.6)	560 (4.1)	<0.001
Missing	0	288 (2.1)	
Psychotropic medication ^h (yes)	883 (1.1)	211 (1.5)	<0.001
Missing	487 (0.6)	516 (3.8)	
Paternal information			
Age, y	33.7 (5.9)	33.0 (6.2)	<0.001
Age category			<0.001
≤24 y	3828 (4.5)	556 (4.1)	
25–34 y	42,717 (50.7)	4287 (31.2)	
≥35 y	34,797 (41.3)	3016 (22.0)	
Missing	2969 (3.5)	5869 (42.8)	
Education			<0.001
High school or less	35,788 (42.5)	6237 (45.4)	
Vocational school/College	18,799 (22.3)	2600 (18.9)	
University or higher	28,342 (33.6)	3420 (24.9)	
Missing	1382 (1.6)	1471 (10.7)	
Child's information			
Sex (boys)	43,217 (51.3)	7023 (51.2)	0.935

Gestational age at birth, week	38.9 (1.3)	38.3 (2.7)	<0.001
Birth weight, g	3042.3 (382.7)	2913.8 (577.7)	<0.001
Placental weight, g	560.5 (105.5)	556.9 (169.5)	0.001
Chest circumference, cm	31.8 (1.6)	31.3 (2.7)	<0.001
Head circumference, cm	33.2 (1.4)	32.8 (2.2)	<0.001
Chest-to-head circumference ratio ⁱ	95.8 (4.0)	95.4 (15.3)	<0.001

^a Results of Student's *t*-test 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 ratio, <10th percentile; normal ratio, 10–90th percentile; high ratio, >90th percentile.

Table S4. Rate of developmental delay (% of children) from 6 to 36 months of age by chest-to-head circumference ratio (Boys).

Age (months)	Normal	Low		High
	Rate (95% confidence interval) ^a			
Communication				
6	1.86 (1.70–2.01)	2.07 (1.64–2.49)		2.34 (1.76–2.92)
12	4.34 (4.11–4.58)	4.58 (3.95–5.21)		3.93 (3.17–4.69)
18	2.88 (2.68–3.08)	3.73 (3.14–4.32)	**	2.82 (2.16–3.49)
24	5.40 (5.13–5.66)	6.02 (5.30–6.74)		5.64 (4.74–6.54)
30	10.01 (9.66–10.36)	11.89 (10.91–12.88)	†	10.60 (9.38–11.82)
36	7.91 (7.60–8.23)	9.45 (8.57–10.33)	†	8.36 (7.28–9.44)
Gross motor				
6	1.81 (1.66–1.97)	2.14 (1.71–2.57)		1.72 (1.21–2.22)
12	5.09 (4.83–5.34)	7.12 (6.35–7.90)	†	4.86 (4.01–5.71)
18	4.43 (4.19–4.68)	6.78 (6.00–7.55)	†	4.23 (3.42–5.05)
24	5.53 (5.26–5.79)	7.48 (6.70–8.27)	†	5.58 (4.68–6.49)
30	4.77 (4.52–5.02)	6.43 (5.69–7.16)	†	4.53 (3.70–5.36)
36	4.89 (4.64–5.14)	5.88 (5.18–6.58)	**	4.01 (3.24–4.79)
Fine motor				
6	2.63 (2.45–2.81)	3.35 (2.82–3.89)	**	2.60 (1.99–3.21)
12	7.07 (6.77–7.37)	8.24 (7.41–9.07)	**	6.80 (5.82–7.79)
18	4.54 (4.30–4.79)	5.31 (4.62–6.01)	*	4.58 (3.74–5.43)
24	5.64 (5.37–5.91)	6.94 (6.18–7.71)	†	5.84 (4.92–6.76)
30	7.84 (7.52–8.16)	8.86 (8.00–9.72)	*	7.73 (6.66–8.80)
36	7.60 (7.29–7.90)	8.11 (7.29–8.93)		8.10 (7.03–9.18)
Problem solving				
6	3.87 (3.65–4.09)	5.09 (4.44–5.74)	†	3.47 (2.76–4.17)
12	6.08 (5.80–6.36)	6.44 (5.70–7.18)		5.55 (4.65–6.44)
18	4.72 (4.47–4.98)	5.44 (4.73–6.14)	*	5.10 (4.21–6.00)
24	4.65 (4.40–4.89)	5.76 (5.06–6.46)	**	5.02 (4.16–5.87)
30	7.70 (7.39–8.02)	8.86 (8.01–9.72)	**	8.25 (7.16–9.35)
36	9.30 (8.96–9.64)	10.42 (9.50–11.34)	*	10.73 (9.51–11.94) *
Personal-social				
6	1.64 (1.50–1.79)	2.00 (1.58–2.42)		1.27 (0.84–1.71)
12	3.58 (3.36–3.80)	3.84 (3.26–4.42)		3.77 (3.02–4.51)
18	5.48 (5.21–5.75)	6.12 (5.38–6.86)		5.03 (4.15–5.90)
24	8.00 (7.68–8.31)	9.99 (9.09–10.88)	†	8.50 (7.42–9.59)
30	8.77 (8.44–9.11)	10.36 (9.44–11.28)	†	8.52 (7.41–9.62)
36	8.69 (8.36–9.01)	9.64 (8.76–10.53)	*	9.24 (8.11–10.37)

Compared with the normal-ratio group: * $p < 0.05$; ** $p < 0.01$; † $p < 0.001$.

^a 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 S5. Rate of developmental delay (% of children) from 6 to 36 months of age by chest-to-head circumference ratio (Girls).

Age (months)	Normal	Low		High	
	Rate (95% confidence interval) ^a				
Communication					
6	1.93 (1.77–2.09)	1.93 (1.51–2.34)		1.67 (1.16–2.17)	
12	2.03 (1.87–2.20)	2.81 (2.31–3.32)	**	2.01 (1.44–2.58)	
18	1.35 (1.21–1.50)	1.60 (1.21–1.99)		1.21 (0.76–1.67)	
24	1.90 (1.73–2.06)	2.23 (1.77–2.68)		2.25 (1.65–2.86)	
30	3.39 (3.17–3.61)	4.02 (3.41–4.63)	*	3.44 (2.68–4.19)	
36	2.75 (2.56–2.95)	3.53 (2.97–4.10)	**	2.86 (2.18–3.54)	
Gross motor					
6	1.59 (1.44–1.73)	2.54 (2.07–3.02)	†	1.94 (1.39–2.49)	
12	5.86 (5.58–6.14)	8.81 (7.95–9.67)	†	6.46 (5.46–7.46)	
18	4.51 (4.26–4.77)	5.47 (4.76–6.17)	**	3.55 (2.78–4.32)	*
24	5.36 (5.10–5.63)	6.60 (5.84–7.36)	**	4.46 (3.62–5.31)	
30	3.36 (3.14–3.57)	4.39 (3.75–5.02)	†	3.06 (2.35–3.78)	
36	3.52 (3.30–3.74)	4.24 (3.62–4.86)	*	2.79 (2.12–3.47)	
Fine motor					
6	2.52 (2.34–2.70)	3.18 (2.65–3.71)	*	2.46 (1.85–3.08)	
12	4.51 (4.26–4.75)	5.38 (4.69–6.06)	*	3.86 (3.08–4.64)	
18	3.97 (3.73–4.21)	4.18 (3.55–4.81)		3.89 (3.09–4.70)	
24	4.42 (4.18–4.67)	5.34 (4.65–6.03)	**	3.71 (2.93–4.48)	
30	3.26 (3.04–3.47)	3.80 (3.21–4.39)		3.11 (2.39–3.83)	
36	2.31 (2.13–2.49)	2.43 (1.95–2.90)		2.27 (1.66–2.88)	
Problem-solving					
6	3.71 (3.49–3.93)	4.57 (3.94–5.20)	**	3.43 (2.71–4.15)	
12	4.15 (3.91–4.39)	5.45 (4.76–6.15)	†	4.40 (3.57–5.23)	
18	3.13 (2.92–3.35)	3.63 (3.04–4.22)		2.86 (2.17–3.56)	
24	3.37 (3.15–3.58)	3.96 (3.36–4.56)		2.97 (2.28–3.67)	
30	3.02 (2.82–3.23)	3.56 (2.99–4.13)		3.46 (2.70–4.21)	
36	4.60 (4.35–4.85)	5.00 (4.33–5.67)		4.77 (3.90–5.65)	
Personal-social					
6	1.04 (0.92–1.16)	1.52 (1.15–1.88)	**	0.61 (0.30–0.92)	*
12	2.32 (2.14–2.50)	3.03 (2.50–3.55)	**	2.11 (1.53–2.70)	
18	2.84 (2.64–3.04)	3.28 (2.72–3.84)		2.76 (2.08–3.44)	
24	3.38 (3.17–3.60)	4.10 (3.49–4.71)	*	3.50 (2.75–4.26)	
30	2.91 (2.70–3.11)	3.44 (2.88–4.01)		3.28 (2.54–4.01)	
36	2.30 (2.12–2.48)	3.24 (2.70–3.78)	†	2.53 (1.88–3.17)	

Compared with normal-ratio group: * $p < 0.05$; ** $p < 0.01$; † $p < 0.001$.

^a 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 S6. Pearson correlation coefficients among anthropometric measurements of 84,311 children at birth.

Measurement	Mean (SD)	1	2	3	4	5
1. Head circumference, cm	33.2 (1.4)	1.00				
2. Chest circumference, cm	31.8 (1.6)	0.60	1.00			
3. Birthweight, g	3042.3 (382.7)	0.60	0.81	1.00		
4. Placental weight, g	560.5 (105.5)	0.38	0.48	0.59	1.00	
5. Chest-to-head circumference ratio	95.8 (4.0)	-0.24	0.63	0.40	0.21	1.00

All Bonferroni-adjusted $p < .001$.

Table S7. Bivariate association of anthropometric measurements with risk of developmental delay in the first 3 years in a lesser-risk population^a.

	Low			High		
	RR	z	95%CI	RR	z	95%CI
<u>Birthweight^b</u>						
Boys						
Communication	1.16	1.96	1.00–1.34	0.91	–1.31	0.79–1.05
Gross motor	1.15	1.76	0.98–1.35	0.99	–0.15	0.86–1.13
Fine motor	1.10	1.46	0.97–1.24	0.89	–1.96	0.80–0.99
Problem solving	1.11	1.66	0.98–1.25	0.93	–1.37	0.83–1.03
Personal-social	1.12	1.72	0.98–1.27	0.87	–2.34	0.78–0.98
Girls						
Communication	1.30	2.49	1.06–1.60	0.99	–0.15	0.81–1.20
Gross motor	1.28	3.04	1.09–1.49	1.06	0.80	0.92–1.22
Fine motor	1.21	2.45	1.04–1.40	0.93	–1.01	0.81–1.07
Problem solving	1.19	2.32	1.03–1.39	0.96	–0.59	0.83–1.10
Personal-social	1.18	1.64	0.97–1.43	0.97	–0.29	0.82–1.16
<u>Chest circumference^b</u>						
Boys						
Communication	1.23	3.39	1.09–1.39	0.97	–0.47	0.84–1.11
Gross motor	1.28	3.82	1.13–1.45	0.99	–0.17	0.86–1.14
Fine motor	1.12	2.27	1.02–1.24	0.91	–1.65	0.81–1.02
Problem solving	1.17	3.01	1.06–1.29	0.97	–0.59	0.86–1.08
Personal-social	1.18	3.09	1.06–1.30	0.95	–0.89	0.85–1.06
Girls						
Communication	1.21	2.16	1.02–1.44	0.85	–1.65	0.69–1.03
Gross motor	1.31	4.14	1.15–1.49	0.92	–1.12	0.79–1.07
Fine motor	1.14	2.07	1.01–1.30	0.91	–1.29	0.79–1.05
Problem solving	1.18	2.56	1.04–1.34	0.87	–1.83	0.76–1.01
Personal-social	1.23	2.53	1.05–1.44	0.89	–1.23	0.75–1.07
<u>Head circumference^b</u>						
Boys						
Communication	1.03	0.45	0.92–1.15	1.14	2.00	1.00–1.30
Gross motor	1.04	0.70	0.93–1.17	1.16	2.10	1.01–1.32
Fine motor	1.12	2.55	1.03–1.22	0.99	–0.00	0.90–1.12
Problem solving	1.02	0.39	0.93–1.12	1.07	1.18	0.96–1.20
Personal-social	1.09	1.81	0.99–1.19	1.02	0.38	0.91–1.15
Girls						
Communication	1.06	0.64	0.89–1.25	1.03	0.28	0.85–1.25
Gross motor	0.95	–0.85	0.83–1.08	1.25	3.12	1.09–1.43
Fine motor	1.08	1.29	0.96–1.22	0.98	–0.33	0.85–1.12
Problem solving	0.96	–0.62	0.85–1.09	1.00	0.00	0.87–1.15
Personal-social	0.97	–0.36	0.83–1.14	1.06	0.67	0.89–1.27

^a n = 62,308; excluding children born preterm, small for gestational age, and those delivered by cesarean section.

^b 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.