

Original Article

Optimisation of birth weight and growth in the first 2 years favours an adult body composition which supports more physiological resting metabolic rates and cognitive function : Tanjungsari Cohort Study (TCS)

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Background and Objectives: Resting metabolic rate and cognitive function may be associated with several factors, such as birth weight, growth, and fat-free mass in adulthood. The Tanjungsari Cohort Study (TCS) of 1988, to do with a maternal-child Risk Approach Strategy (RAS), provided the opportunity to determine the associations between birth weight, growth at 2 years, and body composition with adult resting metabolic rate and cognitive function. **Methods and Study Design:** In 2009 some 197 and, in 2017, 144 of these representative participants from the TCS were assessed for energy intake, anthropometry, body composition, indirect calorimetry, and cognitive function in relation to low (ALBW, n=66) or normal (ANBW, n=78) birth weight. Associations were adjusted for basic demographic data. **Results:** Resting metabolic rate was positively associated with birth weight, body weight at 2 years of age, body mass index and fat free mass in adult life. Time to finish the Trail Making Test-A (TMT-A), a test of attention span, was significantly longer in the ALBW than the ANBW group (41.4±12.8 vs 37.8±15.6, $p=0.005$). In the ALBW group, weight catch-up improved TMT-A and logical memory test scores (29.5 vs 34.9, $p=0.004$; and 39.3 vs 29.4, $p=0.04$, respectively). **Conclusions:** Low birth weight was associated with poorer attention span in adult life; body weight gain at 2 years of age with better attention and memory function in adult life; a greater body mass index in adult life with better memory in adult life.

Key Words: birth weight, growth at 2 years, body composition, resting metabolic rate, attention, memory

INTRODUCTION

Resting metabolic rate (RMR), which represents 80% of total energy expenditure in most (adult) sedentary individuals, is a predictive factor for the occurrence of future weight gain.^{1,2} A meta-analysis on formerly obese individuals revealed a 3%–5% lower RMR than in the control group, suggesting the potential for weight regain in the formerly obese individuals.¹ Obesity is an important public health epidemic linked to adverse health consequences including cardiovascular disease, type 2 diabetes, dementia and malignant disorders.^{3,4}

Among the factors affecting RMR are birth weight and fat-free mass in adulthood.⁵ Birth weight is a critical factor influencing health in later life. Results of studies on the relationships between birth weight and RMR remain inconclusive, however. In the Pima Indian study and a cohort study conducted in Helsinki, birth weight was proven to be negatively associated with RMR.^{5–8} Con-

versely, a study in a Caucasian population in Southampton, the United Kingdom, showed that birth weight was positively associated with RMR.⁹ (Figure 1)

Rapid (catch-up) weight gain in early childhood is independently and consistently associated with fat mass and fat-free mass.¹⁰ Several studies have demonstrated that fat-free mass is strongly correlated with RMR, whereas studies linking catch-up in early growth with RMR are

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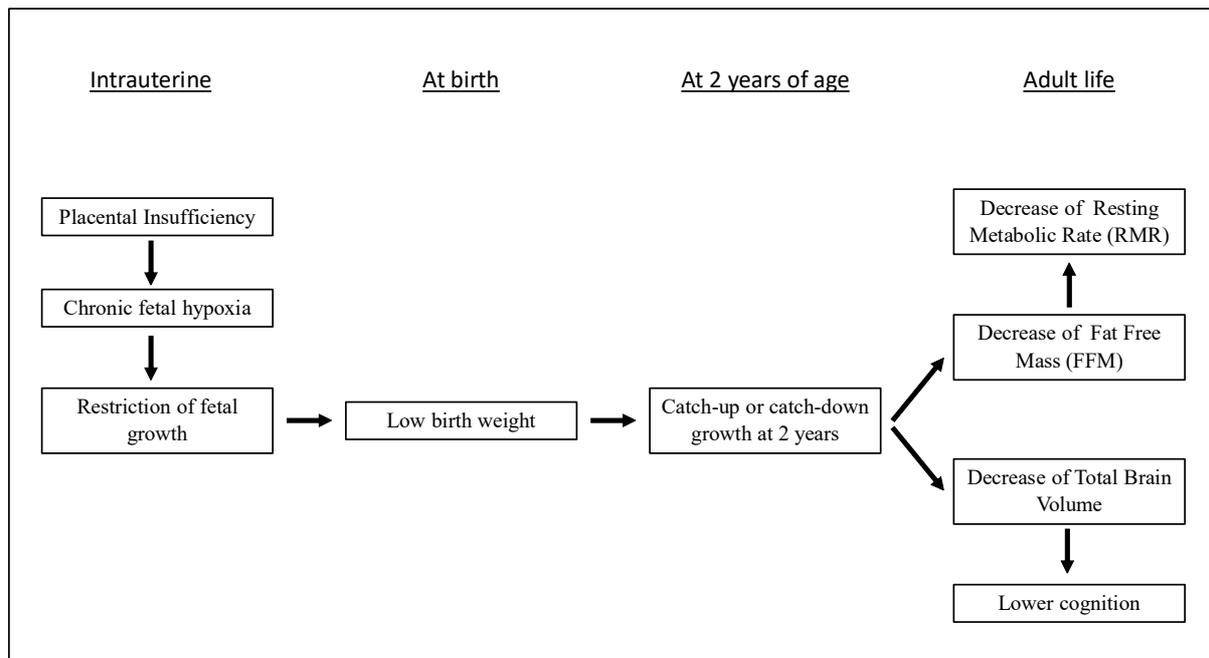


Figure 1. TCS conceptual framework for birth weight, growth at 2 years, resting metabolic rate (RMR) and cognition

relatively few.^{5,10,11} Obesity is known to have an association with low RMR; however, the results obtained by studies have been inconsistent. Several longitudinal studies reported associations between low RMR during childhood and adulthood with later weight gain and obesity development.^{12,13} However, other studies did not identify this association.^{14,15}

The association between birth weight and cognition has been clearly demonstrated by population-based studies.¹⁶⁻¹⁹ Four studies have revealed a positive linear relationship across the whole range of birth weights. A 1997–1999 birth cohort study conducted in Denmark explored the correlation between birthweight and cognitive function in 4300 young adults, and a strong relationship was identified between cognitive function and birthweight for weights of up to 4200 g (adjusted for gestational age), birth length, and other variables.¹⁶

Many early studies have found associations between LBW and poor cognitive performance.²⁰⁻²³ Infants with LBW (birth weight <2500 g), very low birth weight (VLBW, <1500 g), and extremely low birth weight (ELBW, <1000 g) are considered to have a higher risk of attention deficit,^{22,23} executive function disorder,^{16,24,25} and low-average to borderline intelligence quotient (IQ).²⁶⁻²⁹ Cohort studies have demonstrated that more than 50% of adolescents with ELBW had learning difficulties (in mathematics, writing, reading, or spelling), and the effect of LBW accounted for a $0.4 \times$ standard deviation (SD) decrease in mathematics scores and $0.25 \times$ SD decrement in reading scores.^{30,31} Such cognitive disadvantages, in turn, may lead to low school achievement and may persist into early adulthood,³²⁻³⁵ resulting in low socioeconomic status in the future.¹⁸ The association between cognitive deficit and LBW was further confirmed by a recent meta-analysis on 12,137 participants, which reported that the weighted mean difference in IQ score between normal birth weight (NBW) and LBW individuals was 10 (95% CI 9.26–11.68).²¹

The understanding of the pathophysiology of cognitive impairment in low birth weight has grown rapidly. Placental insufficiency is considered the principal cause of intrauterine growth retardation (IUGR).^{36,37} Placental insufficiency results in chronic fetal hypoxemia, reduced nutrient availability and fetal hypoglycemia,³⁶ which in turn decreases fetal growth rate.³⁸ The growth-restricted fetus responds to the chronic hypoxia with slowing its growth rate, and redistributing cardiac output to favour essential organs such as brain (brain sparing).^{38,39}

Post-natal catch-up growth, defined as growth velocity greater than the median for a given age and sex following a period of growth inhibition, is the consequence of an infant being born with weight in a lower centile than the infant's genetic potential.^{40,41} Catch-up growth in the first 2 years has certain advantages; it causes superior neurodevelopment, enhanced immune function, and a taller final adult height. The association between catch-up growth and cognitive function is still somewhat unclear. A cohort study conducted in the United Kingdom on 3418 children with gestational age at birth less than 36 weeks reported that birthweight and postnatal weight gain in the first 2 years of life were positively associated with cognitive and educational attainment at the age of 10 years.³⁵ Another study from Guatemala discovered that early postnatal growth (0–2 years), but not prenatal or late postnatal growth, predicts women's later educational achievements.⁴²

Most of these studies were focused on the intelligence quotient (IQ) of severe low birth weight individuals (VLBW and ELBW), while studies which specifically focused on the effects of moderate low birth weight (MLBW) on cognitive function were rare. Also, the use of specific-domain neuropsychological tests may enable us to pick-up cognitive domains changes which are sensitive to chronological given growth period such as catch-up growth in early life and its effect on adult life cognition.

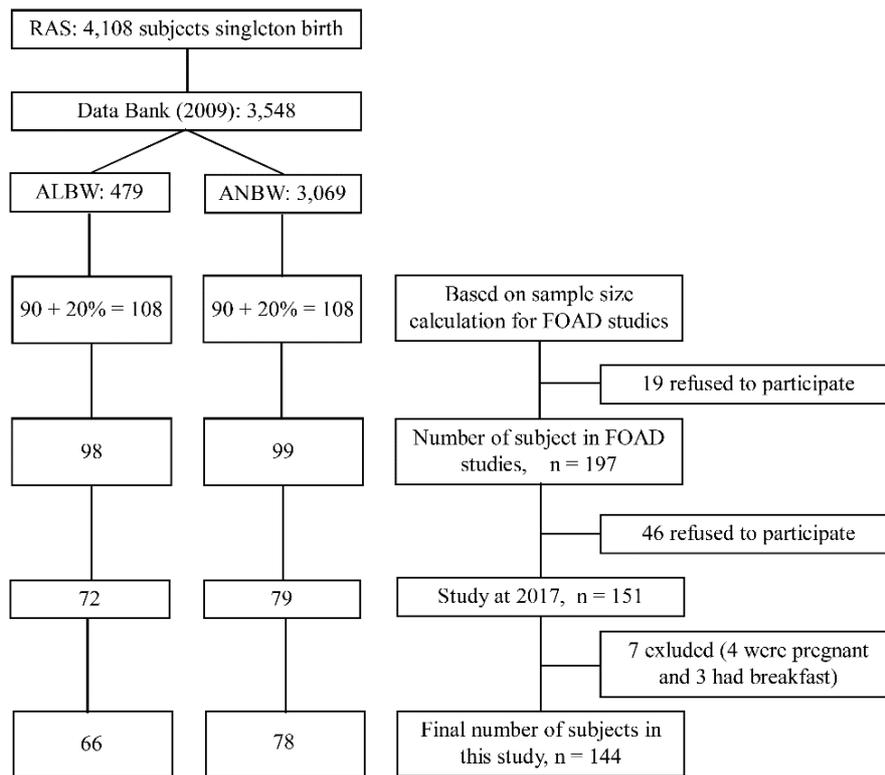


Figure 2. Flowchart of subject selection from the maternal-child RAS of 1988 which provided the TCS follow-ups from 2009 (RMR) to 2017 (Cognitive function). RAS: The Risk Approach Strategy; ALBW: adult with history of low birth weight; ANBW: adult with history of normal birth weight; FOAD: fetal origin of adult disease; low birth weight <2500 g.

The present study was conducted to determine the association between birth weight, growth period at the age of 2 years, and body composition with RMR and investigated whether there existed a specific cognitive deficit in adult with history of LBW (2000–2499 g) as compared with adult with history of NBW (≥ 2500 g). The study also evaluated the effect of weight gain and catch-up at 2 years of age in adult life, on the cognitive function of adults.

The Tanjungsari Cohort Study (TCS) is a longitudinal study that was initiated by The Risk Approach Strategy (RAS) study, a mother-newborn cohort study in 1988.^{43–45} In 2017, the newborn generation reached adult age, thus allowing studies to observe the journey from birth to adulthood. (Figure 2).

MATERIALS AND METHODS

Sample sizes for RMR in 2009 and cognitive function in 2017

We calculated the appropriate sample size based on the Fetal Origin of Adult Diseases study (FOAD) by using a one-sided test, resulting in 180 participants to be divided into two groups: low and normal birth weight.^{46–48} For the presumed and defined reasons (loss to follow-up, exclusion criteria, and refusal to participate in the study), added 20% to our calculations, resulting in 216 participants. Of the estimated 216 participants, 19 refused to participate in the study, leaving a total of 197 participants for final analyses for RMR. Figure 2 illustrates the flow chart of subject recruitment starting from the Risk Approach Strategy (RAS) study and its subsequent derivative studies including the current TCS.⁴³

Recruitment of the subjects

The ultimate participant recruitment was undertaken in 2017. They were considered eligible to this study if they were involved in the FOAD study in 2009 and residing in Tanjungsari Subdistrict, Sumedang District, West Java Province, Indonesia. Of the total 151 subjects of 2017 study agreed to join,⁴⁶ seven adults were excluded from this study. Therefore, 144 subjects were finally included in the cognitive function study, consisting of 66 adults with a low birth weight history (ALBW) and 78 adults with a normal birth weight history (ANBW).

Participants were excluded if they were pregnant or unwilling to follow all the prerequisites before their physical examination. Prerequisites included fasting for 12 hours and abstaining from smoking, drinking alcohol, and consuming caffeinated drinks 4 hours prior to the examination. Additionally, the participants were not permitted to exercise within 2 hours of the examination or to consume any sort of laxative lactulose drug in preceding 24 hours. Any participants who took analgesic drugs within 1 hour of their examination were also excluded. Well trained community health workers or cadres (*kaders*), who were involved in the FOAD study, contacted participants by visiting their homes, which were spread out over 27 villages within Tanjungsari Subdistrict, based on the recorded addresses provided by the GIN. Prior to assessments of body composition, metabolic indicators, and neuropsychological assessment, verbal consent to join the research was obtained.

The overall study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine of Universitas Padjadjaran, Number 16/UN6.C.10/PN/2018.

Body composition and metabolic assessments

Participants who stated their consent to join the research were subsequently taken to the metabolic laboratory of the Faculty of Medicine, Universitas Padjadjaran, according to the previously determined schedule. They underwent clinical examination consisting of measurements of blood pressure, anthropometry, body composition (fat mass and fat-free mass), indirect calorimetry, and total energy intake. Birth weight history and growth at 2 years of age were obtained from previous TCS data.⁴³ Determination of catch-up at the age of 2 years is described in a previous report.⁴⁹ Anthropometric and blood pressure measurements were performed using standard techniques as reported elsewhere.⁵⁰ Body weight, fat mass, and fat-free mass were measured using a tetrapolar bioelectrical impedance analysis scale (TANITA SC-240 MA, Tanita Health Equipment HK Ltd., Kowloon, Hong Kong), whereas height was measured using a stadiometer (SECA 204, SECA GmbH, Hamburg, Germany). All anthropometric measurements were conducted twice, and a third measurement was made only in the instance that the difference between the first two measurements exceeded 0.1 kg or 0.1 cm for weight and height, respectively. The measurement results were recorded on an electronic anthropometry form using a computer.

RMR was measured using indirect calorimetry (QUARK RMR, Cosmed, Rome, Italy). The measurements were performed in a quiet room, and all patients used a hood canopy. During the test, the patient lay down and was asked to not fall asleep. Measurements were recorded at 5-s intervals for 16 min. Calibration was performed prior to every examination. Oxygen consumption (VO_2) and the production of carbon dioxide (VCO_2) in litres per minute, as well as the tidal volume, were measured. RMR values were obtained in kilocalories (kcal) per day by using the Weir Formula: $[3.941 (VO_2) + 1.106 (VCO_2)] \times 1440$. The respiratory coefficient (RQ) was

calculated as $RQ = (VCO_2 / VO_2)$.¹¹ Total energy intake was measured using a semiquantitative food frequency questionnaire.⁵⁰

Neuropsychological assessment

This study focused on attention, memory, visual-motor speed, and executive function, and these variables have been documented in previous studies.²⁸⁻³⁰ Neuropsychological tests were administered in the Indonesian language. Attention was assessed using the Trail Making Test-A (TMT-A). Visuospatial function was assessed using the constructional praxis test. Memory was assessed using verbal word lists (immediate and delayed recall and recognition tests) and recall of constructional praxis tests. Visuomotor function was assessed using the Digit Symbol Substitution Test (DSST). Executive functioning was assessed using the Animal Fluency Test and Trail Making Test-B (TMT-B).

Statistical analyses

Data was analyzed using SPSS software version 23. All variables were described in mean \pm SD or mean rank. Data normality were analyzed using Kolmogorov-Smirnov. Linear regression was used to determine the effect of demographic and clinical data on RMR and cognitive domain scores.

RESULTS

Of the 197 subjects who participated in the 2009 study, 151 people still resided in Tanjungsari and gave their consent to participate in the follow-up study. However, prior to the examination, it was determined that four women were pregnant, and that three people ate breakfast the morning prior to their examination (one exclusion criterion), resulting in 144 people being examined (74 men and 70 women). No significant differences were identified between ALBW and ANBW groups regarding

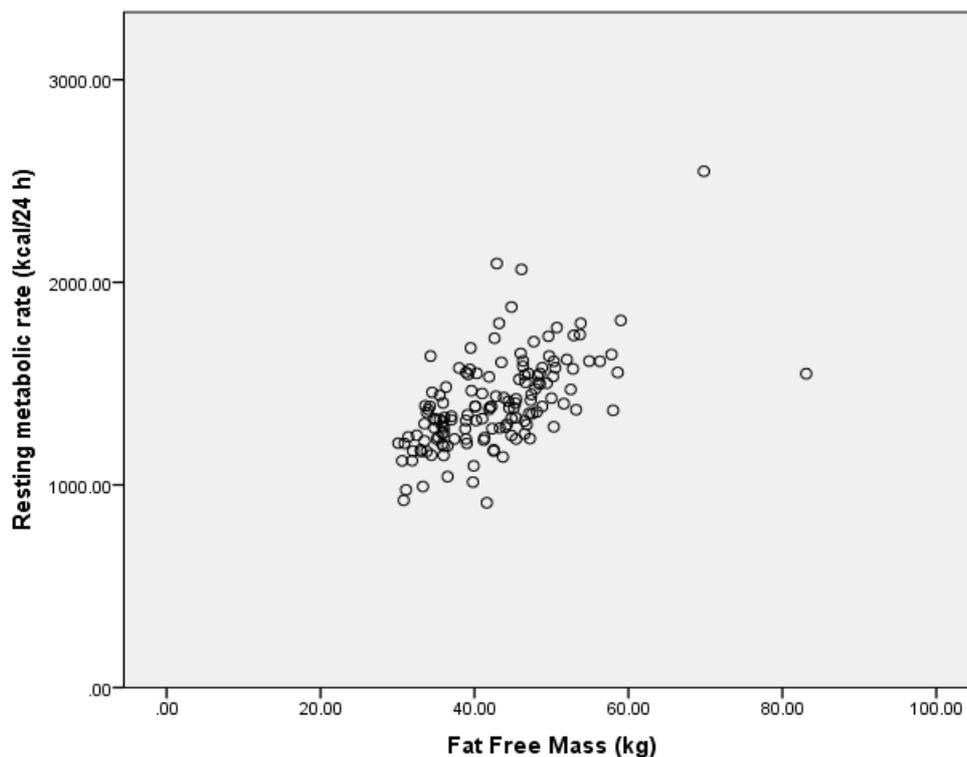
Table 1. Clinical characteristics of participants

Characteristics	Men			Women		
	Mean	SD	Min-Max	Mean	SD	Min-Max
At birth						
Birth weight (kg)	2.7	0.45	2-3.8	2.6	0.25	2.1-3.4
Birth length (cm)	46.9	2.33	41-52	46.1	2.56	41-54
WAZ	-1.5	1.05	-3.21-0.89	-1.6	0.86	-2.81-0.36
HAZ	-1.6	1.22	-4.69-1.12	-1.7	1.4	-4.37-2.60
At 2 years of age						
Weight (kg)	10.3	1.09	6.5-12.3	9.9	1.10	8-13
Height (cm)	78.3	3.56	67-87	77.5	3.99	65-86
WAZ	-0.8	1.46	-4.73-2.51	-1.3	1.48	-3.62-2.93
HAZ	-3.1	1.14	-6.73- -0.30	-2.8	1.22	-6.58- -0.17
Adult life						
Age (years)	28.4	0.64	27-30	28.3	0.58	27-29
Weight (kg)						
Height (cm)	163.9	5.08	153-176	151.9	5.44	141-164
Body mass index (kg/m ²)	21.1	3.69	15.1-36.8	24.4	4.63	16.2-36.5
Waist circumference (cm)	74.1	9.98	61-109	80.8	11.57	59-115
Fat mass (kg)	9.6	8.54	1.40-51.5	19.5	8.56	4.6-42
Fat free mass (kg)	48.4	6.58	39.00-83.10	36.8	4.03	30.1-51.6
Resting metabolic rate (kcal/24 h)	1459.3	224.8	912-2548	1346.1	219.18	924-2093
Total energy intake (kcal/day)	2242.6	526.4	1142.4-4012.9	1802.2	457.27	821.7-3039.3

WAZ: weight for age z-score; HAZ: height for age z-score.

Table 2. RMR (kcal/24 h) in men and women according to birth weight, catch-up at 2 years, and BMI in adult life

	Men		Women	
	Mean (SD)	n	Mean (SD)	n
Birth weight				
Low birth weight (<2500 g)	1409.9 (187.6)	27	1317.0 (219.1)	39
Normal birth weight (≥2500 g)	1495.5 (243.9)	47	1392.3 (215.3)	31
<i>p</i> value for trend	0.09		0.16	
2 years age				
Body weight				
Catch-up	1409.3 (197.2)	33	1403.7 (233.0)	27
No change	1463.8 (188.6)	27	1277.6 (143.3)	24
Catch-down	1570.4 (311.6)	14	1350.7 (261.2)	19
<i>p</i> value for trend	0.07		0.12	
Body height				
Catch-up	1549.4 (157.6)	7	1499.5 (258.5)	12
No change	1558.7 (305.5)	17	1401.6 (254.8)	21
Catch-down	1413.4 (187.1)	50	1264.8 (138.4)	37
<i>p</i> value for trend	0.04*		0.001*	
Adult life				
Body mass index				
Underweight (≤18.5)	1308.0 (189.7)	17	1249.5 (245.6)	6
Normal (18.6-22.9)	1466.5 (162.7)	42	1257.0 (146.9)	25
Overweight (≥23)	1612.1 (303.0)	15	1418.0 (231.7)	39
<i>p</i> value for trend	<0.0001*		0.007	

p*<0.05.Figure 3.** Correlation between RMR and fat-free mass in adulthood ($r=0.62$, $p<0.001$).

demographic data. Birth weight, body weight, body length and WAZ at 2 years age were significantly lower in the ALBW than ANBW group. In adult life, body weight, body height, fat free mass and resting metabolic rate were lower in the ALBW than ANBW group. (Table 1).

There were 27 men (41.9% of the men) and 39 women (61.4% of the women) with low birth weight. No significant difference was discovered in the RMR between birth

weight groups among the men or women. At 2 years age, height was associated with RMR; in adulthood, BMI was associated with RMR (Table 2).

In further analysis, we discovered a moderate positive correlation between RMR and fat-free mass ($r=0.62$, $p<0.001$), as shown in Figure 3.

Linear regression analyses were performed to estimate the association of clinical characteristics with RMR, and these analyses were adjusted for sex and fat mass (Table

Table 3. Association between clinical characteristics at birth, 2 years, in adulthood and RMR

Clinical characteristic	Resting metabolic rate, kcal/24 hours (not adjusted)		Resting metabolic rate, kcal/24 hours (adjusted) [†]	
	β (95%CI)	<i>p</i> value	β (95%CI)	<i>p</i> value
Birth				
Birth weight (g)	0.2 (0.09, 0.27)	<0.001*	0.2 (0.09, 0.16)	0.03*
Birth length (cm)	-2.9 (-18.7, 12.4)	0.71	-9.5 (-22.2, 7.9)	0.13
WAZ	70.4 (32.9, 107.9)	<0.001*	34.8 (3.10, 66.6)	0.03*
HAZ	-12.0 (-41.38, 17.4)	0.42	-13.9 (-41.1, 5.17)	0.13
2 years of age				
Weight (kg)	83.2 (52.1, 114.4)	<0.001*	34.0 (4.58, 63.5)	0.02*
Height (cm)	21.1 (11.7, 30.5)	<0.001*	10.8 (2.67, 18.9)	0.01*
WAZ	40.7 (16.1, 65.3)	0.001*	8.8 (-12.7, 30.2)	0.42
HAZ	54.8 (24.2, 85.4)	0.001*	34.4 (8.4, 60.5)	0.01*
Adult life				
Age (years)	18.8 (-42.3, 79.9)	0.54	7.9 (-40.8, 56.7)	0.75
Weight (kg)	14.7 (12.3, 17.1)	<0.001*	18.0 (13.5, 22.6)	<0.001*
Height (cm)	12.0 (7.7, 16.3)	<0.001*	12.8 (7.5, 18.2)	<0.001*
Body mass index (kg/m ²)	24.8 (17.4, 32.2)	<0.001*	29.0 (14.7, 43.3)	<0.001*
Waist circumference (cm)	9.9 (6.9, 12.8)	<0.001*	12.5 (9.73, 15.2)	<0.001*
Fat free mass (kg)	16.8 (12.9, 20.7)	<0.001*	15.9 (9.23, 22.7)	<0.001*
Total energy intake (kcal)	0.1 (-0.01, 0.12)	0.14	0.0 (-0.03, 0.09)	0.32

WAZ: weight for age z-score; HAZ: height for age z-score.

[†]Adjusted by sex and fat mass.

Table 4. Comparison of neuropsychological test scores between ALBW and ANBW groups

Neuropsychological tests	ALBW	ANBW	<i>p</i> value
MoCA-Ina score	26.2±2.85	26.4±2.68	0.85
Attention			
TMT-A (time in seconds, max 180)	41.4±12.8	37.8±15.6	0.005*
Visuomotor speed			
Symbol digit modalities task (no. correct in 90 seconds, max 110)	47.2±12.3	45.5±9.32	0.44
Visuospatial			
Constructional praxis (no. correct, max 11)	10.9±0.56	10.9±0.41	0.34
Memory			
Logical memory (no. correct, max 21.5)	9.01±3.31	8.68±2.87	0.75
Wordlist, immediate recall (no. correct, max 30)	21.7±2.75	21.3±2.97	0.62
Wordlist, delayed recall (no. correct, max 10)	8.49±1.07	8.71±0.99	0.17
Wordlist, recognition (true positive minus false positive)	10.0±0.12	9.90±0.91	0.16
Recall of constructional praxis (no. correct, max 14)	12.3±2.48	12.8±2.35	0.28
Language			
Boston naming (no. correct, max 15)	13.0±1.35	13.2±1.51	0.83
Executive function			
Animal fluency (no. of words in 60 seconds)	20.3±5.43	19.9±4.78	0.78
TMT-B (time in seconds, max 300)	76.4±35.6	70.8±33.3	0.20

ALBW: Adult with history of low birth weight; ANBW: Adult with history of normal birth weight; MoCA-Ina: The Montreal cognitive assessment-Indonesian version; TMT-A: Trail making test-A; TMT-B: Trail making test-B.

**p*<0.05

3). We found that birth weight and weight at 2 years age were positively associated with RMR. In adult life, body mass index and fat free mass positively associated with RMR.

In multiple regression analysis including all clinical characteristics and sex, the significant independent determinants of RMR were fat mass, fat-free mass, body height, and BMI in adult life, which together explained 62% of the variability.

Table 4 shows a comparison of the neuropsychological test results between the two groups. No significant differences were discovered in the results of the global cognitive screening test, the montreal cognitive assessment-indonesian version (MoCA-Ina) or domain-specific cognitive tests between the two groups except in the domain

of attention (TMT-A), for which the score was significantly lower in the ALBW group.

Table 5 shows that in the ALBW group, subjects who experienced catch-up at 2 years performed better on attention and memory tests. They took shorter times to finish the TMT-A, a test of attention, and they had higher scores on the logical memory test. Conversely, the catch-up subjects in the ANBW group performed more poorly on visuospatial function, as indicated by their lower scores on the constructional praxis test. The global cognitive screen test score (MoCA-Ina) and the scores of other cognitive domains were unaffected by weight catch-up in both the ALBW and ANBW groups.

Table 6 summarises the associations between body weight and body length/height at the three time points;

Table 5. Comparison of neuropsychological test scores between catch-up and non-catch-up subjects

Neuropsychological tests	ALBW			ANBW		
	Catch up	Non catch up	<i>p</i> value	Catch up	Non catch up	<i>p</i> value
MoCA-Ina score	37.3	33.1	0.38	35.7	40.2	0.42
Attention						
TMT-A (time in seconds, max 180)	29.5	43.5	0.004*	39.5	38.8	0.90
Visuomotor speed						
Symbol digit modalities task (no. correct in 90 seconds, max 110)	36.0	34.9	0.82	38.6	39.2	0.92
Visuospatial						
Constructional praxis (no. correct, max 11)	35.3	34.6	0.74	36.3	40.0	0.02*
Memory						
Logical memory (no. correct, max 21.5)	39.3	29.4	0.04*	38.7	39.1	0.95
Wordlist, immediate recall (no. correct, max 30)	37.2	32.1	0.29	41.4	38.1	0.56
Wordlist, delayed recall (no. correct, max 10)	34.1	36.2	0.65	37.1	39.7	0.62
Wordlist, recognition (true positive minus false positive)	34.5	35.7	0.25	39.5	38.8	0.54
Recall of constructional praxis (no. correct, max 14)	37.3	32.1	0.24	35.6	40.3	0.36
Language						
Boston naming (no. correct, max 15)	32.6	39.4	0.16	36.0	40.1	0.46
Executive function						
Animal fluency (no. of words in 60 seconds)	35.7	35.3	0.94	38.9	39.2	0.99
TMT-B (time in seconds, max 300)	31.6	40.8	0.06	37.4	39.6	0.69

ALBW: Adult with history of low birth weight; ANBW: Adult with history of normal birth weight; MoCA-Ina: The Montreal cognitive assessment-Indonesian version; TMT-A: Trail making test-A; TMT-B: Trail making test-B.

**p*<0.05.

vascular risk factors; and the results of neuropsychological tests for attention and memory. Regarding attention, LBW and body weight at age 2 years were inversely associated with adult attention scores on the TMT-A. Regarding memory, LBW was not associated with memory score in adulthood (logical memory test); however, body weight and weight catch-up at age 2 years, as well as body weight and BMI in adult life, were positively associated with memory score (logical memory test).

DISCUSSION

In this study, no demographic differences were discovered between the ALBW and ANBW groups except for sex; there were more women in the ALBW group than the ANBW group (Table 1). Previous VLBW and ELBW studies have reported that cognitive disadvantages may lead to low school achievement in early adulthood and low socioeconomic status in the future,^{18,32-35} in our study, ALBW had the same level of education, employment, monthly income and marital status compare to those ANBW. Briefly, this is reasonable since all of our LBW subject were categorized as moderate LBW, with mean body weight of 2310.12±142.47, approaching to the cut off of NBW 2500 g. Thus, we may suppose that our ALBW subjects might have much milder cognitive deficit and managed to catch-up in education and social economic attainment at adult life, whereas the reported VLBW and ELBW subjects did not.

The mean birth weight of the participants was more than 2500 g. Fat-free mass correlated moderately with RMR. The clinical characteristics discovered to be associated with RMR were birth weight; weight at 2 years of age; and BMI and fat-free mass in adult life. Some cohort studies have shown that birth weight is positively associated with fat-free mass in adult life.^{51,52} Moreover, in adult subjects, fat-free mass was shown to be positively

correlated with RMR.⁴ The result of the present study is in agreement with those of previous studies; fat-free mass was positively correlated with RMR, and birth weight was positively associated with RMR. These results differ from those obtained by two studies with Caucasian participants, however, which showed that birth weight was negatively correlated with RMR.⁴ This difference is likely because the range of birth weights in the previous studies was relatively wide (2000–5000 g), whereas in our study it was 2000–3800 g. We did not identify any increase in sympathetic nervous system activity in people with low birth weight, a finding which contrasts with previous evidence.⁵³

At the age of 2 years, there is a 'catch-up' trend in height both in men and women of higher RMR compared with their 'no change' or 'catch-down' counterparts. Weight, height, weight z-score, and height z-score at age of 2 years were found to be associated with RMR. Fat-free mass is a factor independently associated with RMR, so fat-free mass can be considered a surrogate for RMR. The findings of this study indicate that body size (weight and height) at 2 years of age is a crucial factor determining RMR during adulthood; thus, improving nutritional status that affects body size at this age (i.e. catch-up) may independently affect RMR in adulthood regardless of birth weight. The results of this study are consistent with those of a cohort study in Guatemala with similar characteristics.⁵³ In addition to similar mean height z-scores at the age of 2 years (−2.7 for men and −2.5 for women, which indicate stunting), the Guatemala study discovered that a child's height at 2 years was positively associated with their fat-free mass at 20–27 years of age.⁴⁹

All clinical characteristics—body weight, height, BMI, fat mass, fat-free mass, and blood pressure—were found to be associated with RMR. These results are consistent

Table 6. Multiple linear regression models for TMT-A and logical memory on early life and adult weight

Anthropometry	TMT-A Not adjusted		TMT-A Adjusted [†]		Logical memory Not adjusted		Logical memory Adjusted [†]	
	β (95% CI)	<i>p</i> value	β (95% CI)	<i>p</i> value	β (95% CI)	<i>p</i> value	β (95% CI)	<i>p</i> value
Birth weight	-0.20 (-0.01, -0.00)	0.01*	-0.18(-.012, -.001)	0.03*	0.001 (-0.00, 0.001)	0.99	-0.010 (-0.001, 0.001)	0.90
Body weight at 2 years of age	-0.29 (-0.01, -0.00)	<0.001*	-0.26 (-0.005, -.001)	0.002*	0.16 (0.00, 0.001)	0.04*	0.195 (0.000, 0.001)	0.02*
BMI at adult life	-0.01 (-0.57, 0.50)	0.89	-0.12 (-0.98, 0.19)	0.18	0.23 (0.05, 0.27)	0.006*	0.222 (0.035, 0.274)	0.01*

[†]Adjusted by age, education, sex, monthly income, and marital status **p*<0.05.
TMT-A is Trail making test-A.

with the findings of a Brazilian study showing that body weight, BMI, and fat-free mass are positively associated with RMR.¹¹ Studies in Brazil and Finland obtained a similar finding that fat-free mass is positively associated with RMR, thus indicating that fat-free mass is a variable that can act as a surrogate for RMR in adults.^{5,10} This study also showed that even our ALBW participants had the same achievement for education level, socioeconomic attainment and the global cognitive screening test compared to their ANBW counterparts. But they had lower scores for specific cognitive domain tests of attention compared to those with ANBW. These subtle cognitive deficits in attention were significant in adult life (41.4 ± 12.8 vs 37.8 ± 15.6 , $p=0.005$) (Table 3). The importance of attention performance should be emphasized, since attention as part of working memory is crucial for high cognitive load occupations, where even a slight impairment in attention may hamper or reduce work performance. In the present study, ALBW had a lower attention performance compared with ANBW.

Aside from the known attention deficits in the ALBW group, analysis of catch-up at 2 years of age in both groups revealed its role in influencing cognitive achievement. In the ALBW group, catch-up was associated with superior attention and memory function compared with their counterparts who did not experience catch-up growth; this was reflected in the shorter time it took catch-up subjects to finish the TMT-A, and by the higher score that the catch-up participants obtained on the logical memory test (29.5 vs 43.5 , $p=0.004$ and 39.5 vs 38.8 , $p=0.9$, respectively). By contrast, the catch-up subjects in the ANBW group showed poorer visuospatial function, as reflected by their lower scores on the constructional praxis test (36.3 vs 40.0 , $p=0.02$; Table 4). These two findings indicated that weight catch-up may be a modulating factor for birth weight and cognitive achievement.

To find whether the modulation of attention and memory scores was not confounded by basic demographic characteristics, adjustments were made for age, gender, monthly income, and marital status (Table 4). ALBW was still associated with lower attention scores; furthermore, subjects with weight gain at 2 years of age also obtained higher attention scores, but this association was diminished in adult life. Even though memory was not associated with birth weight, this cognitive domain did exhibit a significant association with body weight gain and catch-up at 2 years of age, and this association persisted through to adulthood (Table 4).

Attention refers to the ability to attend to a specific stimulus without being distracted by extraneous environmental stimuli. Attention represents complex interactions between wide areas of the brain such as the limbic system, neocortex, and ascending reticular activating system, together with their susceptibilities.⁵⁴ The mechanism by which attention deficit is linked to LBW is unclear. In animal models, as in rodents, chronic malnutrition appears to alter cell numbers, cell migration, myelination, synaptogenesis, hippocampal formation, and neurotransmission.^{55,56} An autopsy study of humans found fewer neurons with shorter dendrites and abnormal dendritic spines in protein energy malnutrition (PEM).⁵⁷ Our identification of an association between attention deficit and

LBW is in agreement with recent studies of intrauterine growth restriction with fetal maturation, which potentially leads to cerebral immaturity at birth.⁵⁸⁻⁶¹

Memory is a general term for the mental process that allows an individual to store perceptions and experiences for recall at a later time. The logical memory test is a test of immediate recall (of verbal stories) as well as a means of evaluating the ability to learn new information.⁵⁴ Recent memory requires intact limbic structures (hippocampi, the mammillary bodies, and the dorsal medial nuclei of the thalami) and their links to subcortical structures to ensure storage in and retrieval of information from the cortex.⁵⁴

Our study demonstrated that weight gain and catch-up was associated with superior memory performance in subjects with LBW. Several mechanisms may explain this. First, optimal nutrition during pregnancy and the first 2 years of life is vital for normal growth and brain development, so that nutritional deficits may have long-term implications for cognitive function.⁶² Second, insulin-like growth factor and growth hormone—which both play a critical role in determining somatic growth—and the receptors of insulin-like growth factor are widely expressed in regions of the brain that are responsible for learning and memory, specifically the limbic structures and frontal lobes.⁶³ In children born small for gestational age, growth hormone therapy has demonstrated the capacity to promote catch-up growth as well as improvements in IQ score.⁶⁴

Strengths and Limitations

Although the TCS indicates that there are cognitive benefits with weight catch-up, caution should be taken in interpreting these findings because catch-up may also increase vascular risk factors such as hyperglycaemia and increased waist circumference, as well as BMI.

A strength of the present study has been its use of multiple factor analysis at different time points: at birth (weight and height), at 2 years of age (anthropometry), and in adult life (RMR using indirect calorimetry). For cognitive function, the present study focussed on moderate low birth weight (ALBW) for individual and global cognitive tests. Cohort studies, such as TCS allow longitudinal research with some understanding of potential causality and policy relevance, especially when representative or whole-of-community, which is how the Tanjungsari RAS was originally devised. In addition, indirect calorimetry to measure RMR as an outcome measure is a rarity in developing countries.

A limitation has been the a reduced number of available participants as the TCS has progressed to 2009 and 2017. Again, although known to have been a generally socioeconomically disadvantaged cohort at its inception, considerable sociodemographic change and alteration in equity has occurred over the 3 decades of the TCS, which have not been taken into account in the analyses. In conclusion, in the TCS birth weight, body weight at age 2, BMI and fat free mass in adult life are associated with reduced RMR and lower attention scores in adulthood than those found among their ANBW counterparts. Weight gain and catch-up at 2 years of age were associated with better attention and memory function in adult-

hood. Optimisation of nutritional status as judged by early childhood growth in LBW children and catch-up may allow higher RMRs to reduce the risk of overfatness and otherwise impaired cognitive function.

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AUTHOR DISCLOSURES

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