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Original Article

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Physique at Birth and Cardiovascular Disease Risk Factors in Japanese Urban Residents: the KOBE Study

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Aim: This study investigated the relationship between birth physique and cardiovascular risk factors in Japanese urban residents aged 40 years and more.

Methods: A self-administered questionnaire on birth physique was performed among 624 individuals (165 men and 459 women) who participated in the KOBE study. We examined whether self-reported birth physique and available recorded birth weights matched for 72 participants. Then the association between birth physique and risk factors for all participants was examined by gender. Body size at birth in the questionnaire (large, medium, small) was set as an exposure and laboratory values from the baseline survey (2010-2011) were used as outcomes.

Results: Mean (standard deviation) recorded birth weight of 72 participants was 3665 (318), 3051 (300), and 2653 (199) g, in the large, medium, and small group, respectively. In the analysis for all participants, odds ratio for having both hypertension and impaired glucose tolerance were significantly higher in the small versus large birth weight group, which was 7.42 (95% CI 1.75–31.50) for men and 4.44 (95% CI 1.14–17.30) for women after adjusting for age, body mass index, smoking/alcohol/exercise habits, and menstrual status in women. Similar results were observed in participants with recorded birth weight.

Conclusions: The present study indicates that individuals with small physique at birth might be at higher risk for hypertension and impaired glucose tolerance in middle age compared to those with large birth weight.

Key words: Physique at birth, Birth weight, Hypertension, Impaired glucose tolerance, Epidemiologic study

Introduction

Hypertension, dyslipidemia, and glucose intolerance are classic risk factors for cardiovascular disease (CVD) and are well known lifestyle diseases. Lifestyle diseases develop early in the life course and

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the intrauterine environment is an important factor. According to the Developmental Origins of Health and Disease (DOHaD) hypothesis, the interaction between fetal factors and the environment is thought to influence a person's health and life, and in the process determine disease[1-3].

A study of Taiwanese schoolchildren revealed a U-shaped relationship between birth weight and risk of type II diabetes[4], with epidemiological studies of children and adolescents in Europe and South Korea showing a negative correlation between birth weight and systolic and diastolic blood pressure and insulin resistance[5-8].

Although the causes of lifestyle diseases are thought to vary in risk depending on subsequent lifestyle habits such as age, body mass index (BMI), physical activity, and smoking, epidemiological studies in Europe and China in middle age and older patients suggest that birth weight is negatively associated with risk of developing hypertension, diabetes, and coronary artery disease[9-20], with a number of associations between birth weight and risk having been reported.

Previous studies in Japan have also investigated a possible correlation between birth weight and risk factors for CVD, but this association is conflicting and largely unknown in the Japanese population.

Aim

The present study investigated the relationship between birth physique, the self-reported hearsay memory of the size of the body at birth based on questionnaire and cardiovascular risk factors in adulthood in Japanese urban residents aged 40 years and more, which was the typical age of onset for lifestyle-related diseases such as CVDs. We also examined whether self-reported birth physique and available recorded birth weights matched for 72 participants.

Methods

3.1 Participants

This study examined participants in the KOBE study, an urban resident cohort study, for which the details have previously been reported elsewhere[21-27]. In brief, the KOBE study comprised a baseline survey conducted from 2010–2011 with 1134 participants who were subjectively healthy residents of Kobe City, who were aged 40–74 years, who had no history of CVD or malignant tumors, and who were not undergoing treatment for hypertension, dyslipidemia, or diabetes. After the 2010-2011 baseline assessment, a two-year inspection cycle was initiated.

Of the 896 participants who were followed for a third time in 2017-2018, we excluded 18 participants who did not return their birth weight questionnaires, 241 who did not remember their birth weight, and 13 who did not have the data required for this study.

Finally, 624 individuals (165 males and 459 females) were included in the analysis (Fig. 1).

3.2 Method of Determining Birth Physique

The method of determining birth physique was based on an approach in a previous study (Suita Study)[28]. Birth physique was defined according to the self-reported hearsay memory of the size of the body at birth by a self-administered questionnaire, and participants were asked to select one of the following size descriptors for their physique at birth: "large"; "medium"; "small"; or "unknown." No medical definitions of these birth weight descriptions were offered to the participants. To investigate questionnaire reproducibility, the same questionnaire was administered again in June 2019 to 59 participants who were administered the survey in May 2017.

We also request that participants submitted their maternal and child health handbook or commemorative box containing umbilical cord stump (usually birth weight was recorded by doctors or medical staffs) to the survey site. The 77 participants who brought them were interviewed by a researcher (K.U., a midwife) at a separated booth independent from other booths for medical examination, and the birth weight information was transcribed from such items. Then, the relationship between the recalled physiques "large," "medium," and "small," and the actual birth weight was compared. Furthermore, we performed an additional analysis to examine the relationship between objective birth weight and cardiovascular risk factors.

3.3 Measurement Methods

The gathered information of the baseline survey (2010–2011) was used as CVD risk factors in the present study. The BMI was calculated by multiplying weight (kg) by height in meters squared. Blood pressure was measured using an automated sphygmomanometer (BP-103i II). Measurements were taken twice for each participant after they rested by sitting for five minutes, and the mean values of two measurements were recorded. Blood samples were collected from all participants after 10-hour fasting and then sent to an outsourced clinical testing center (SRL Inc.) for analysis. Latex immunoassay was used to measure HbA1c, and the enzyme method to

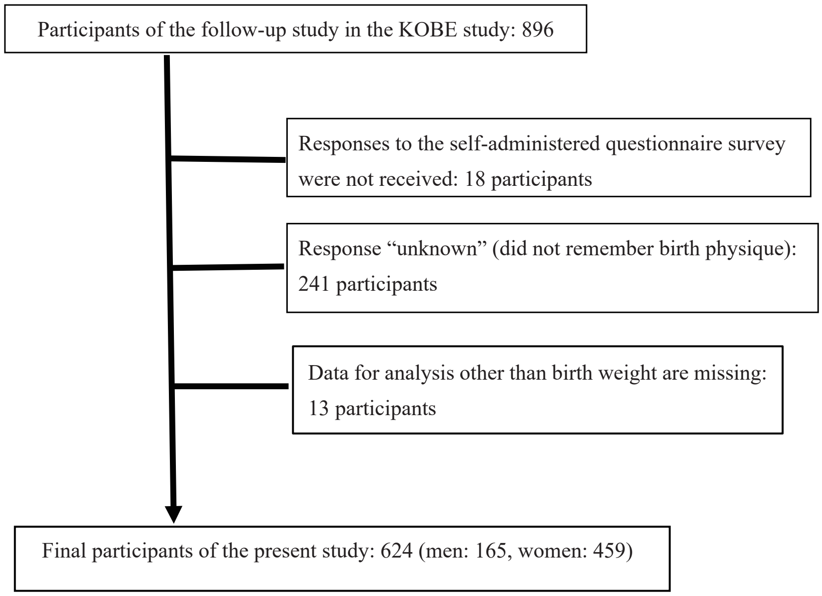

Fig. 1. Selection of study participants

measure total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula[29]. The participants answered a self-administered questionnaire regarding lifestyle-related factors such as smoking history (never habitually smoked; previously smoked, but have now quit; currently smoking), alcohol consumption habit (have never habitually consumed alcohol; previously habitually consumed alcohol but have now quit; currently habitually consume alcohol), exercise habit (habitually and deliberately engage in at least 30 minutes of exercise 2–3 times per week, in addition to the movement required for daily lifestyle; do not engage in habitual walking) and menstrual/menopause status (women only)[30].

High blood pressure was defined as systolic blood pressure (SBP) ≥ 130 mmHg and diastolic blood pressure (DBP) ≥ 80 mmHg, which are diagnostic criteria in the hypertension guidelines for the management of hypertension 2019[31] (Japanese Society of Hypertension). Impaired glucose tolerance was defined as fasting blood glucose ≥ 100 mg/dl or hemoglobin A1c ≥ 5.6% based on the Program for Standard Health Check-ups and Standard Health Guidance (Health Service Bureau, Ministry of Health, Labor and Welfare)[32]. Hypercholesterolemia was defined as LDL ≥ 160 mg/dl according to the lipid management goal for low-risk patients in the primary prevention defined in the Japan Atherosclerosis Society guidelines for prevention of atherosclerotic CVDs 2017[33].

3.4 Statistical Analysis

Kappa coefficient was used to evaluate the reproducibility of the self-administered questionnaire survey. The mean recorded birth weights from the maternal and child health handbook (or other such content made available by the participant) were calculated according to the self-reported birth physique, i.e., "large," "medium," and "small". To investigate associations between birth physique and CVD risk factors, one-way analysis of variance was used for mean values, and the chi-squared test was used to determine prevalence. Data for TG were displayed as median values (interquartile range), and analysis was performed after logarithmic conversion. Multiple logistic regression models were used to analyze the association between birth physique and hypertension, impaired glucose tolerance, hypercholesterolemia, and each comorbid condition of these were performed, adjusting for possible confounding factors.

Odds ratios (ORs) with 95% confidence intervals (CI) were calculated.

The data from participants with objective data on birth weight recorded in a maternal and child health handbook or related sources were used (62 women) to investigate possible correlations between objective birth weight and risk factors. Because of the small sample size, participants were divided into two groups for this analysis based on the first quartile for birth weight: <2700 g and ≥ 2700 g. We did not use

Table 1. Birth weight in Maternal and child health handbook and survey physique

Number of subjects	Overall (n = 72)		Men (n = 10)		Women (n = 62)	
Birth physique	Number (%)	Weight (g) ± SD	Number (%)	Weight (g) ± SD	Number (%)	Weight (g) ± SD
Large	19 (26.4)	3665 ± 318	6 (60.0)	3760 ± 487	13 (21.0)	3621 ± 216
Medium	38 (52.8)	3051 ± 300	4 (40.0)	3178 ± 127	34 (54.8)	3036 ± 312
Small	15 (20.8)	2653 ± 199	0		15 (24.2)	2653 ± 199

SD: standard deviation

data of men due to small sample size (n = 10).

Statistical significance was assumed at $P < 0.05$ and all statistical tests were two-tailed. All data were analyzed using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA).

3.5 Ethical Considerations

This study was approved by the Institutional Review Board (IRB) for Pharmaceutical Research of the Foundation for Biomedical Research and Innovation at Kobe (approval no.: 10-20) and the IRB of the Keio University School of Medicine (approval no.: 20170142). The participants were given written and oral explanations of the study and their consent for participation was received in writing.

Results

4.1 Investigation of Questionnaire Study Reproducibility

A questionnaire of the same 59 participants in May 2017 and June 2019 was administered to investigate the reproducibility of responses for the birth physique. A Kappa coefficient of 0.684 was achieved for large, medium, and small descriptions of birth weight, indicating that results were thought to be fairly consistent.

4.2 Self-Reported Birth Physique and Objective Birth Weight

Maternal and child health handbook or commemorative box containing umbilical cord stump was provided by 77 participants (68 from child health handbook and 9 from commemorative box). However, 5 of the 77 maternal and child health handbook did not include birth weight information. Accordingly, 72 individuals (10 men and 62 women) were included in the present study. A comparison of the mean ± standard deviation (SD) of birth weight in the three birth physique groups (large, medium, and small) in 72 participants showed that the means were in agreement with the rankings of birth physique groups **(Table 1)**.

4.3 Basic Characteristics and Risk Factors by the Birth Physique

The mean age for men was 59.6 years (SD 9.2) and for women was 56.1 years (SD 8.5). A physique at birth for men was large for 32 participants (19.4%), medium for 97 participants (58.8%), and small for 36 participants (21.8%) (Table 2a); for women, it was large for 64 (13.9%), medium for 307participants (66.9%), and small for 88 participants (19.2%).

Among men, means for current height, body weight, BMI, and waist were significantly larger for those who answered “large” than for those who answered “small” **(Table 2a)**. Among women, although height and weight were significantly higher for the participants who answered “large” than for those who answered “small,” no differences were noted for BMI or Waist **(Table 2b)**.

Although the prevalence of high blood pressure tended to increase in order from “large” to “medium” and “small” for women, prevalence for high blood pressure (SBP ≥ 130 or DBP ≥ 80 mmHg), impaired glucose tolerance (fasting blood sugar 100 mg/dL or HbA1c ≥ 5.6%), and hypercholesterolemia (LDL-C ≥ 160 mg/dL) revealed no significant differences according to birth physique for either men or women. Comparison of overlaps of ≥ 2 risk factors revealed that the prevalence of both high blood pressure and impaired glucose tolerance was higher in order from “large” to “medium” to “small” for both men and women with a particularly evident tendency for men.

4.4 Birth Physique and CVD Risk Factors in Multivariable Analysis

Multiple logistic regression analysis was conducted with the presence or absence of risk factors as the dependent variable and birth physique as the independent variable after adjusting for age, BMI, smoking habit, alcohol consumption status, exercise habit, and menstrual/menopause status (women only). Except for hypercholesterolemia, the largest OR for each risk factor was observed in the “small” birth physique group. A statistically significant increase in

Table 2a. Characteristics of study participants: men

Men (n = 165) Number of subjects (%)	Large 32 (19.4) mean ± SD	Medium 97 (58.8) mean ± SD	Small 36 (21.8) mean ± SD	*P* value
Age (years)	58.3 ± 10.4	60.2 ± 9.0	58.8 ± 8.7	0.51
Height (cm)	171.0 ± 5.1	168.0 ± 5.9	166.4 ± 5.1	< 0.01
Body weight (kg)	69.1 ± 10.8	65.9 ± 8.9	59. 5 ± 5.5	< 0.01
BMI	23.6 ± 3.3	23.3 ± 2.8	21.5 ± 2.0	< 0.01
Waist (cm)	84.6 ± 8.4	83.8 ± 8.8	79.7 ± 6.5	< 0.05
Systolic BP (mmHg)	124.6 ± 15.2	121.3 ± 18.2	123.3 ± 17.2	0.60
Diastolic BP (mmHg)	78.9 ± 8.0	78.1 ± 11.2	78.8 ± 10.0	0.89
Fasting BS (mg/dL)	90.7 ± 7.2	92.7 ± 9.6	93.7 ± 10.5	0.40
HbA1c (%)	5.4 ± 0.3	5.5 ± 0.4	5.6 ± 0.6	0.11
HOMA-IR	0.9 ± 0.6	0.9 ± 0.6	0.7 ± 0.3	0.25
Insulin (µU/mL)	4.1 ± 2.7	4.0 ± 2.5	3.2 ± 1.3	0.18
HDL-C (mg/dL)	62.5 ± 15.0	59.2 ± 13.6	65.6 ± 16.1	0.07
LDL-C (mg/dL)	126.1 ± 28.0	122.1 ± 23.2	117.8 ± 29.3	0.41
TG (mg/dL) median	87.0	86.0	85.5	0.75
(interquartile range)	(63.5-129.5)	(57.0–122.0)	(61.0-119.0)	
high blood pressure (SBP ≥ 130 or DBP ≥ 80 mmHg) or higher n (%)	19 (59.4)	45 (46.4)	20 (55.6)	0.36
impaired glucose tolerance (IFG100 mg/dL or HbA1c ≥ 5.6%) n (%)	8 (25.0)	36 (37.1)	15 (41.7)	0.33
Hypercholesterolemia (LDL-C ≥ 160 mg/dl) (%)	4 (12.5)	6 (6.2)	3 (8.3)	0.51
High blood pressure and impaired glucose tolerance n (%)	4 (12.5)	16 (16.5)	13 (36.1)	< 0.05
Impaired glucose tolerance and hypercholesterolemia n (%)	2 (6.3)	4 (4.1)	0 (0)	0.36
High blood pressure and hypercholesterolemia n (%)	2 (6.3)	0 (0)	1 (2.8)	0.06
Alcohol consumption status n (%)				
Have never habitually consumed alcohol	7 (21.9)	15 (15.5)	6 (16.7)	0.68
Previously habitually consumed alcohol but do not currently	0 (0)	5 (5.2)	2 (5.6)	
Currently consume alcohol	25 (78.1)	77 (79.4)	28 (77.8)	
Smoking status n (%)				
Have never habitually smoked	14 (43.8)	42 (43.3)	14 (38.9)	0.95
Used to smoke but have now quit	16 (50.0)	45 (46.4)	18 (50.0)	
Currently smoke	2 (6.3)	10 (10.3)	4 (11.1)	
Exercise n (%)				
Have a habit of walking	21 (65.6)	55 (56.7)	21 (58.3)	0.67
Do not have a habit of walking	11 (34.4)	42 (43.3)	15 (41.7)	

SD: standard deviation
BMI, body mass index; BP, blood pressure; BS, blood sugar; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride
Exercise, Continuously walk for at least 30 minutes, 2-3 times per week as exercise not required during daily lifestyle

OR in the "small" group compared with the "large" group was observed for elevated blood pressure for women (OR 2.65, 95% CI 1.03–6.86) **(Table 3)**. When the analysis was performed with risk overlapping as the dependent variable, in both men and women, the OR for having both high blood pressure and impaired glucose tolerance was significantly higher for the "small" group (OR for men 7.42, 95% CI 1.75–31.50; OR for women 4.44, 95% CI 1.14–17.30) when the "large" group was set as a reference **(Table 3)**.

4.5 Investigation of Participants for whom Birth Weight could be Objectively Obtained

Since birth weight was able to be objectively confirmed for 62 women, sub-group analysis was performed. The first quartile for these women's birth weight was almost the same as the mean objective birth weight in the "small" birth physique group. Due to small sample size, analysis of participants after dividing them by birth weight into the first quartile (< 2700 g) or other participants (≥ 2700 g) was performed, which revealed that values for current height and body weight were significantly larger in the

Table 2b. Characteristics by birth physique: women

Women (n = 459) Number of subjects (%)	Large 64 (13.9) mean ± SD	Medium 307 (66.9) mean ± SD	Small 88 (19.2) mean ± SD	P value
Age (years)	57.2 ± 9.4	55.9 ± 8.3	56.1 ± 8.5	0.52
Height (cm)	159.0 ± 4.9	156.6 ± 5.1	153.8 ± 5.2	< 0.01
Body weight (kg)	53.4 ± 6.8	51.0 ± 7.1	49.6 ± 6.4	< 0.01
BMI	21.2 ± 2.4	20.8 ± 2.6	21.0 ± 2.4	0.47
Waist (cm)	79.7 ± 7.4	77.9 ± 8.6	77.5 ± 7.1	0.20
Systolic BP (mmHg)	110.9 ± 15.6	112.7 ± 16.1	113.0 ± 16.6	0.68
Diastolic BP (mmHg)	67.6 ± 9.7	69.3 ± 10.6	70.1 ± 11.2	0.35
Fasting BS (mg/dL)	86.3 ± 7.1	88.0 ± 6.8	87.8 ± 6.9	0.20
HbA1c (%)	5.5 ± 0.3	5.5 ± 0.3	5.6 ± 0.3	0.28
HOMA-IR	0.7 ± 0.3	0.8 ± 0.5	0.8 ± 0.4	0.31
Insulin (µU/mL)	3.2 ± 1.4	3.5 ± 1.9	3.6 ± 1.7	0.34
HDL-C (mg/dL)	73.1 ± 16.2	71.5 ± 15.1	73.2 ± 16.3	0.55
LDL-C (mg/dL)	129.3 ± 30.4	132.8 ± 28.7	135.0 ± 25.7	0.48
TG (mg/dL) median	68.0	69.0	76.0	0.34
(interquartile range)	(44.5–98.5)	(54.0–97.0)	(56.5–102.0)	
Menopause n (%)	46 (71.9)	219 (71.3)	65 (73.9)	0.89
High blood pressure (SBP ≥ 130 or DBP ≥ 80 mmHg) or higher n (%)	8 (12.5)	61 (19.9)	20 (22.7)	0.27
impaired glucose tolerance (IFG100 mg/dL or HbA1c ≥ 5.6%) n (%)	23 (35.9)	124 (40.4)	37 (42.0)	0.73
Hypercholesterolemia (LDL-C ≥ 160 mg/dl) n (%)	8 (12.5)	56 (18.2)	12 (13.6)	0.38
High blood pressure and impaired glucose tolerance n (%)	3 (4.7)	32 (10.4)	12 (13.6)	0.20
impaired glucose tolerance and hypercholesterolemia n(%)	5 (7.8)	23 (7.5)	4 (4.5)	0.61
High blood pressure and hypercholesterolemia n (%)	2 (3.1)	14 (4.6)	2 (2.3)	0.58
Alcohol consumption status n (%)				
Have never habitually consumed alcohol	40 (62.5)	170 (55.3)	54 (61.4)	0.16
Previously habitually consumed alcohol but do not currently	1 (1.6)	6 (2.0)	5 (5.7)	
Currently consume alcohol	23 (35.9)	131 (42.7)	29 (33.0)	
Smoking status n (%)				
Have never habitually smoked	57 (89.1)	280 (91.2)	78 (88.6)	0.52
Used to smoke but have now quit	7 (10.9)	21 (6.8)	9 (10.2)	
Currently smoke	0 (0.0)	0 (0.0)	1 (1.1)	
Exercise n (%)				
Have a habit of walking	33 (51.6)	159 (51.8)	39 (44.3)	0.46
Do not have a habit of walking	31 (48.4)	148 (48.2)	4 (4.5)	

SD: standard deviation
BMI, body mass index; BP, blood pressure; BS, blood sugar; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride
Exercise, Continuously walk for at least 30 minutes, 2-3 times per week as exercise not required during daily lifestyle

"≥ 2700 g" group **(Table 4)**. Although age-adjusted logistic regression did not reveal any significant differences between the first quartile and other quartiles because of the small number of participants, the ORs for high blood pressure and impaired glucose tolerance tended to be higher in the "< 2700 g" group than those in the "≥ 2700 g" group **(Table 5)**.

Discussion

This study investigated the possible association between birth physique and cardiovascular risk factors after middle-age among urban residents in Japan. Our findings revealed that smaller birth physique in both men and women tended to be associated with a higher prevalence of high blood pressure and impaired glucose tolerance, especially the coexistence of these. No such association was observed for hypercholesterolemia. The results for the birth physique used in this study were based on a self-reported questionnaire. However, using the same approach of a previous study[28], self-reported birth physique was confirmed by objective

Table 3. Multiple regression analysis of birth physique and cardiovascular disease risk factors: odds ratio and 95% confidence interval

Sex	Birth physique	High blood pressure		impaired glucose tolerance		Hypercholesterol-emia		High blood pressure and impaired glucose tolerance		impaired glucose tol-erance and hypercho-lesterolemia		High blood pressure and hypercholesterol-emia	
		OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Overall (*n* = 624)	Large: standard group (*n* = 96)	1.00		1.00		1.00		1.00		1.00		1.00	
	Medium (*n* = 404)	1.16	(0.66, 2.04)	1.51	(0.61, 4.01)	1.34	(0.67, 2.66)	2.31	(0.97, 5.53)	1.08	(0.44, 2.66)	1.05	(0.30, 3.55)
	Small (*n* = 124)	1.80	(0.93, 3.50)	1.77	(0.98, 3.20)	1.01	(0.43, 2.35)	5.12	(1.97, 13.25)	0.46	(0.13, 1.66)	0.80	(0.16, 3.98)
Men (*n* = 165)	Large: standard group (*n* = 32)	1.00		1.00		1.00		1.00		1.00		1.00	
	Medium (*n* = 97)	0.55	(0.22, 1.39)	1.56	(0.61, 4.01)	0.51	(0.12, 2.17)	1.39	(0.40, 4.84)	0.91	(0.12, 6.90)	0	(0, 0)
	Small (*n* = 36)	1.23	(0.41, 3.73)	2.53	(0.82, 7.75)	0.63	(0.12, 3.44)	7.42	(1.75, 31.50)	0	(0, 0)	0.45	(0.03, 7.72)
Women (*n* = 459)	Large: standard group (*n* = 64)	1.00		1.00		1.00		1.00		1.00		1.00	
	Medium (*n* = 307)	2.13	(0.92, 4.96)	1.46	(0.80, 2.64)	2.02	(0.88, 4.63)	2.96	(0.84, 10.40)	1.35	(0.47, 3.93)	2.50	(0.47, 13.30)
	Small (*n* = 88)	2.65	(1.03, 6.86)	1.57	(0.77, 3.19)	1.29	(0.48, 3.35)	4.44	(1.14, 17.30)	0.66	(0.16, 2.66)	1.24	(0.15, 10.40)

SD: standard deviation
Adjusted for: Age, BMI, alcohol consumption, smoking, exercise, menopause (women); overall analysis adjusted for sex
High blood pressure: SBP ≥ 130 mmHg or DBP ≥ 80 mmHg; impaired glucose tolerance: IFG ≥ 100 mg/dL or HbA1c ≥ 5.6%; hypercholesterolemia: LDL-C ≥ 160 mg/dL
①Alcohol consumption: Never habitually consumed alcohol (standard group)/Previously habitually consumed alcohol but currently do not/Currently consume alcohol
②Smoking: Have never habitually smoked (standard group)/Previously smoked but quit/Currently smoke
③Exercise habit: Have a habit of consciously walking for 30 minutes or longer at least 2-3 times per week for purposes other than daily lifestyle (standard group)/Do not have such a habit

birth weight recorded in the maternal and child health handbooks and other related content provided by some participants; and the sub-group analysis with objective birth weight almost showed similar results.

Previous studies conducted in Japan have indicated associations between birth weight and adverse conditions such as diabetes and hypertension[34-40]. However, few epidemiologic studies have targeted middle-aged populations because most reports have focused on individuals during their childhood or young adulthood.

The Suita Study investigated possible correlations between birth physique and risk factors from middle age onwards in 1241 urban residents (521 men, 720 women). Like the present study, the Suita Study gathered data by asking participants to recall their birth physique in a questionnaire survey; and then confirmed the validity of the interviews by comparing the self-reported physiques of 28 participants with actual birth weights recorded in their maternal and child health handbook. The Suita Study found a significant inverse correlation between birth weight with SBP and DBP in women. Their findings also suggested a high prevalence of diabetes in the “small” birth weight group for women (17.8%), which was higher than those in the “medium” (2.9%) and the

Table 4. Analysis of participants with birth weight confirmed on Maternal and child health handbook or other sources: women

Women (*n*=62)	Birth weight ≥ 2700g	Birth weight < 2700g	
Number of subjects (%)	48 (77.4)	14 (22.6)	
	mean ± SD	mean ± SD	*P* value
Birth weight (g)	3219.5 ± 350.1	2554.4 ± 83.6	
Age (years)	50.3 ± 6.3	51.4 ± 7.8	0.60
Height (cm)	158.1 ± 5.4	154.5 ± 6.1	< 0.05
Body weight (kg)	52.2 ± 7.9	47.9 ± 5.3	< 0.05
BMI	20.8 ± 2.6	20.0 ± 1.9	0.32
Waist (cm)	76.7 ± 9.0	74.3 ± 7.3	0.35
Systolic BP (mmHg)	108.9 ± 12.2	110.7 ± 17.3	0.67
Diastolic BP (mmHg)	69.1 ± 9.4	69.4 ± 10.9	0.91
Fasting BS (mg/dL)	87.1 ± 5.4	87.5 ± 7.5	0.84
HbA1c (%)	5.5 ± 0.3	5.5 ± 0.4	0.63
HOMA-IR	0.7 ± 0.4	0.8 ± 0.4	0.68
Insulin (µU/mL)	3.3 ± 1.6	3.5 ± 1.7	0.70
HDL-C	74.3 ± 14.9	70.0 ± 11.1	0.40
LDL-C (mg/dL)	126.1 ± 31.7	142.4 ± 29.5	0.08
TG (mg/dL) median (interquartile range)	60.0 (44.0–97.5)	73.0 (49.3–4.5)	0.95
Menopause *n* (%)	24 (50.0%)	9 (64.3%)	0.35
High blood pressure (SBP ≥ 130 or DBP ≥ 80 mmHg) or higher *n* (%)	4 (8.3%)	2 (14.3%)	0.51
impaired glucose tolerance (IFG 100 mg/dL or HbA1c ≥ 5.6%) *n* (%)	14 (29.2%)	6 (42.9%)	0.34
Hypercholesterolemia (LDL-C ≥ 160 mg/dl) *n* (%)	8 (16.7%)	4 (28.6%)	0.32

SD: standard deviation
BMI, body mass index; BP, blood pressure; BS, blood sugar; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride

Table 5. Multivariate analysis of birth weight and cardiovascular disease risk factors for participants whose birth weight was confirmed on Maternal and child health handbook (women): odds ratio and confidence interval

Women (*n* = 62)	High blood pressure		impaired glucose tolerance		Hypercholesterolemia	
Birth weight	OR	95%CI	OR	95%CI	OR	95%CI
≥ 2700 g (*n* = 48) :standard group	1.00		1.00		1.00	
< 2700 g (*n* = 14)	1.72	(0.28,19.81)	1.72	(0.48,6.22)	1.80	(0.37,8.93)

1) Adjusted for: Age
2) High blood pressure: SBP ≥ 130 mmHg or DBP ≥ 80 mmHg; impaired glucose tolerance: IFG ≥ 100 mg/dL or HbA1c ≥ 5.6%; Hypercholesterolemia : LDL-C ≥ 160 mg/dL

"large" group (0%), respectively[28]. Therefore, the results of previous studies appeared to be largely consistent with the results of the present study.

In results demonstrating an inverse correlation between birth weight and risk for hypertension during adulthood, looking at studies conducted outside of Japan, a meta-analysis investigating a possible correlation between birth weight and blood pressure during adulthood found that the risk of having hypertension was increased in participants with a low birth weight (<2500 g) compared to those with a birth weight of 2500 g or greater (OR 1.21, 95% CI 1.13–1.30); mean SBP was also increased by 2.28 mmHg (95% CI 1.24–3.33)[41]. A meta-analysis investigating a possible correlation between birth weight and type II diabetes found that diabetes risk was higher when birth weight was low (<2500g vs. ≥ 2500g) (OR 1.51, 95% CI 1.43–1.58)[42]. Although there are differences between birth physique and birth weight as evaluation indicators, the results of the present study appear consistent with those reported for international studies, with previous studies having demonstrated an inverse correlation between birth weight and risk for type II diabetes[42, 43].

Where the Suita Study revealed a significant inverse correlation between birth weight with LDL-C and TC in men, the present study did not reveal any correlations between birth physique and hypercholesterolemia. In a previous meta-analysis, low birth weight was associated with high levels of TC, however, the pooled regression coefficient for an increment in birth weight of 1 kg was relatively small (-0.08 mmol/L, i.e., 3.1 mg/dL)[44]. In another Japanese study, Suzuki *et al.* examined medical students aged 19–31 years. They found that birth weight exhibited inverse correlations with TC and TG in men[45], suggesting a possible association between birth weight and not only TC but also TG. Unfortunately, the reasons for the differences between these studies are unclear. Further study is warranted.

In Japan, there are few studies to investigate correlations between self-reported birth weight or birth physique, and recorded birth weight such as in the maternal and child health handbook in Japan, where, in the Nurses' Health Study II, self-reported birthweights of participants aged 27 to 44 years showed a strong correlation with birthweights recalled by their mothers and with those from state birth records[46]. One study in Japan is the Suita Study and the other is conducted by The Japan Nurses' Health Study. In the Suita Study, maternal and child health handbooks were able to be confirmed for 29 of 1241 (2.3%) participants[28], whereas in the study by The Japan Nurses' Health Study. were confirmed for 24 of 120 (20%) participants, all of whom were female[47]. In contrast, the present study confirmed objective birth weight for 72 of 624 (11.5%) participants, of which number of participants with objective birth weight is largest although proportion of participants with objective birthweight in whole participants is lower than that of The Japan Nurses' Health Study. The mean age of the participants in the present study was 57.0 years, which correlates with a year of birth of 1955–1956. The mean birth weight in Japan for this year range was 3150 g for boys and 3006 g for girls[48]. The mean birth weight in the "medium" group for the present study closely matched the mean birth weight for individuals born in this year range.

There are various causes of birth weight loss, including multiple pregnancies, pre-pregnancy maternal emaciation, under-nutrition to reduce mother's weight gain during pregnancy, smoking, and maternal complications. In Japan, the major reason for the decline in birth weight in Japan may be due to the desire for thinness among young women, with birth weight having been decreasing since the 1980s[49]. The energy intake of Japanese women in their twenties is declining; consequently, 20%-25% of women in this age group have a BMI of less than 18.5[50].

While the current maternal and child health handbook does not describe the relationship between small birth weight and future risk of lifestyle-related diseases, the above-mentioned trend among young Japanese women may accelerate the decline in birth weight, which may increase the risk of CVD in the future. Accordingly, additional education for brides and women who wish to become pregnant, with information about potential risk for small birth physique, can help to improve the health of the next generation.

A strength of the present study was the fact that participants were excluded if they had a history of CVD or malignancy or were being treated for hypertension, dyslipidemia, or diabetes. Moreover, as the participants were in general urban residents they were recruited through a public appeal for the original KOBE study. This population is very healthy, accordingly, current existing critical lifestyle-related diseases and/or treatment for these have little impact on the results of the present study. Sub-group analysis of the participants for whom objective birth weights were available revealed that the correlations between recorded birth weight and risk factors were almost identical to the trends noted for birth physique, although a significant difference was not observed because of small sample size. Finally, suggesting a common pathological cause for both hypertension and impaired glucose tolerance, such as insulin resistance and/or visceral fat accumulation, the present study showed that the smaller the birth physique, the higher the prevalence of coexistence of hypertension and impaired glucose tolerance. Further research should be warranted.

This study has several limitations. Firstly, information on birth physique was asked by self-reported questionnaire, which may include recall bias. However, when the same survey was administered for some of the same participants twice with an interval of two years, good reproducibility was confirmed. Secondly, we did not use real birth weight for all participants, although we tried to check objective birth weight by the maternal and child health handbooks or related materials for 72 participants. Thirdly, being small for gestational age[51-54] may correlate more strongly with future lifestyle-related diseases than birth weight. Unfortunately, in the present study, the research team was unable to investigate this topic. Fourthly, although it has been reported that perinatal status correlates with risk factors for future lifestyle-related diseases[55], the research team was also unable to investigate this correlation and therefore hopes to examine this topic in the future.

Conclusion

These results suggest that a small physique at birth correlates with increased risk for both high blood pressure and impaired glucose tolerance. In the future, to prevent CVD in adulthood for women, effective interventional method at an early stage of pregnancy should be developed to improve the health of the next generation.

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Conflict of Interest

The authors declare no conflicts of interest in association with the study. Financial support was from institutional sources only.

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