Relationships between Birth Weight and Serum Cholesterol Levels in Healthy Japanese Late Adolescents

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Summary Poor growth in utero has been suggested to be associated with adverse levels of serum cholesterol concentrations in later life. In Asia, there have only been a limited number of studies examining the relationship between fetal status and serum lipids, especially in adolescents. The objective of this study was to examine the relationships between birth weight and serum high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels; adjusting for current physical status including percent body fat, physical activity and nutrient intake in healthy Japanese late adolescents. The data of 573 late adolescents with an average age of 17.6 (287 boys and 286 girls) who underwent physical examinations which included blood sampling and who had all the required data, were analyzed. Birth weight was obtained from their maternal and child health handbook. Multiple regression analysis showed that birth weight was positively associated with serum HDL in girls, independently of percent body fat or fat intake, when adjusted for current body height and weight. There were no associations between birth weight and serum HDL in boys, or serum LDL in either sex.

Key Words birth weight, serum cholesterol, body fat, physical activity, Japanese late adolescent

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Materials and Methods

Subjects. We have conducted physical examinations including optional blood sampling of students at a junior and senior high school in Tokyo, Japan, annually in April of each year since 2000. A questionnaire about their birth records was mailed to parents of 2,056 students (1,054 boys and 1,002 girls) who were enrolled at the school in 2005. We obtained data at birth from 1,157 subjects (616 boys and 541 girls). In this study, we analyzed subjects who were born at full term pregnancy (gestational age: from 37 to 41 wk) from a single birth to avoid possible conflicts from pre- or postmaturity or multiple pregnancies. The following subjects were excluded from analysis: 31 subjects who were born before 37 wk or after 41 wk and 3 subjects who were born as twins. Results from the examination in the 3rd year of high school (aged 17 or 18) were used as the current physical status of late adolescents. Finally, 573 subjects (287 boys and 286 girls) who had all the required data were analyzed for this study. The purpose and protocol of this study were explained to the subjects in advance and written informed consent was obtained.
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from each subject. This study was conducted in compliance with the Declaration of Helsinki. The Ethics Committee of Kagawa Nutrition University approved the procedures used in this study.

Measurements. A questionnaire about their birth record asked parents to provide measurements at birth from their maternal and child health handbook. In this study, birth weight was used as a measurement of fetal nutrition status. Body height and weight at the 3rd year of high school were measured to the nearest 0.1 cm and 0.1 kg, respectively, while subjects wore light clothes and no shoes. Body mass index (BMI, weight (kg)/height (m)^2) was calculated. Percent body fat was assessed using a multi-frequency impedance bioelectrical impedance analyzer (BIA, InBody, Biospace Japan Inc., Tokyo, Japan). Serum samples were obtained from blood drawn in the morning under nonfasting conditions. All samples were maintained at a temperature of −20˚C while in transport for measurement at a laboratory in Tokyo (SRL Inc., Tokyo, Japan). Serum HDL and LDL cholesterol levels were measured directly. Dietary intakes during the preceding month were assessed using a self-administered food frequency questionnaire (FFQ) (7). Energy intake (kcal/d), and also protein and fat energy percent intake (% Energy) were calculated on the basis of the Standard Tables of Food Composition in Japan (8). Pearson's correlation coefficients between the FFQ and dietary records were 0.42 for energy (p<0.001), 0.32 for protein (p<0.001) and 0.31 for fat intake (p<0.001). Frequency of physical activity (d/wk) asked as “How many days do you usually exercise in a week besides for school classes?”, and only for girls, their age at menarche were reported in a self-administered lifestyle questionnaire. Menarcheal age (age at the time of the survey minus age at menarche) was also calculated. All the measurements except the questionnaire about birth record were conducted on the same day.

Statistical analysis. Pearson’s product-moment correlation coefficient was calculated to test for linear correlations between birth weight and serum HDL and LDL cholesterol levels with other measures. Multiple regression analysis was used to assess the relationships of serum HDL and LDL cholesterol levels with each measurement. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 19.0 (IBM Japan, Ltd., Tokyo, Japan).

RESULTS

The subjects’ birth weight, and demographic and physical characteristics, serum HDL and LDL cholesterol level, frequency of physical activity and nutrient intakes in the 3rd year of high school are shown in Table 1. The mean±standard deviation (SD) of birth weights were 3.163±0.363 kg for boys and 3.069±0.347 kg for girls. The body height and weight of the subjects were equal to the subjects aged 17 to 18 y that participated in the National Nutrition Survey, Japan (9).

Table 2 shows the correlation coefficients for birth weight and serum HDL and LDL cholesterol levels with other measures. Birth weight correlated positively with body height (r=0.27, p<0.001 for boys and r=0.26, p<0.001 for girls), body weight (r=0.24, p<0.001 for boys and r=0.28, p<0.001 for girls) and BMI (r=0.13, p<0.05 for boys and r=0.18, p<0.01 for girls). Only in boys, birth weight also correlated positively with energy intake (r=0.12, p<0.05). Serum HDL correlated negatively with body weight (r=-0.17, p<0.01 for boys and r=-0.18, p<0.01 for girls), BMI (r=-0.15, p<0.05 for boys and r=-0.14, p<0.05 for girls), percent body fat (r=-0.16, p<0.01 for boys and r=-0.21, p<0.001 for girls) and positively with frequency of physical activity (r=0.29, p<0.001 for boys and r=0.27, p<0.001 for girls) in both sexes. In addition, only in girls, serum HDL also correlated negatively with body weight (r=-0.12, p<0.05) and positively with fat intake (r=0.17, p<0.01). Serum LDL correlated positively with body weight (r=0.22, p<0.001), BMI (r=0.26, p<0.001) and percent body fat (r=0.37, p<0.001) and negatively with frequency of physical activity (r=-0.17, p<0.01) only in boys. There was no significant correlation between serum LDL and the other measurements in girls.

Table 3 shows the results of linear regression models used to examine the relationship between serum HDL or LDL cholesterol levels and other measurements. Predictor variables were birth weight, postmenarcheal age (only for girls), body height, body weight, percent body fat, physical activity, energy intake, protein intake and fat intake in model 1, and birth weight, postmenarcheal age (only for girls), percent body fat, physical activity, energy intake, protein intake and fat intake in model 2. BMI was not included in any of the models because of the high correlation between BMI and percent body fat. In boys, birth weight had no significant association with serum HDL, while a lower body weight

| Variable | Boys (n=287) | Girls (n=286) |
|----------|-------------|---------------|
| Birth weight (kg) | 3.163±0.363 | 3.069±0.347 |
| Age (y) | 17.6±0.3 | 17.6±0.3 |
| Postmenarcheal age (y) | 5.6±1.3 | 5.6±1.3 |
| Body height (cm) | 171.9±5.4 | 158.4±5.0 |
| Body weight (kg) | 63.0±8.2 | 53.0±7.2 |
| BMI (kg/m^2) | 21.3±2.5 | 21.1±2.5 |
| Percent body fat (%) | 14.6±4.4 | 26.0±5.0 |
| Serum HDL (mg/dL) | 59±11 | 67±13 |
| Serum LDL (mg/dL) | 93±23 | 97±23 |
| Physical activity (d/wk) | 3.5±2.6 | 2.1±2.0 |
| Energy intake (kcal/d) | 2,034±486 | 1,674±343 |
| Protein intake (% Energy) | 17.7±2.7 | 18.0±2.8 |
| Fat intake (% Energy) | 31.4±5.0 | 34.7±4.7 |

1 Values are mean±standard deviation.
2 Body mass index.
3 High-density lipoprotein.
4 Low-density lipoprotein.
Table 2. Pearson’s correlation coefficients for birth weight and serum HDL$^1$ and LDL$^2$ cholesterol levels with other measures.

|                  | Boys ($n=287$) | Girls ($n=286$) |
|------------------|----------------|-----------------|
|                  | Birth weight (kg) | Serum HDL$^1$ (mg/dL) | Serum LDL$^2$ (mg/dL) | Birth weight (kg) | Serum HDL$^1$ (mg/dL) | Serum LDL$^2$ (mg/dL) |
|                  | $r^3$ $p$       | $r^3$ $p$       | $r^3$ $p$       | $r^3$ $p$       | $r^3$ $p$       | $r^3$ $p$       |
| Birth weight (kg) | — —             | 0.05 0.42       | -0.04 0.50      | — —             | 0.10 0.10       | -0.11 0.08      |
| Postmenarcheal age (y) | — —     | — —             | — —             | — —             | — —             | — —             |
| Body height (cm)  | 0.27 <0.001     | -0.08 0.19      | -0.05 0.42      | 0.26 <0.001     | -0.12 <0.05     | -0.11 0.06      |
| Body weight (kg)  | 0.24 <0.001     | -0.17 <0.01     | 0.22 <0.001     | 0.28 <0.001     | -0.18 <0.01     | 0.01 0.82       |
| BMI$^4$ (kg/m$^2$) | 0.13 <0.05      | -0.15 <0.05     | 0.26 <0.001     | 0.18 <0.01      | -0.14 <0.05     | 0.07 0.21       |
| Percent body fat (%) | -0.07 0.22     | -0.16 <0.01     | 0.37 <0.001     | -0.03 0.67      | -0.21 <0.001    | 0.11 0.07       |
| Serum HDL$^1$ (mg/dL) | 0.05 0.42      | — —             | -0.15 <0.05     | 0.10 0.10       | — —             | — —             |
| Serum LDL$^2$ (mg/dL) | -0.04 0.50     | -0.15 <0.05     | — —             | -0.11 0.08      | 0.05 0.42       | — —             |
| Physical activity (d/wk) | 0.04 0.46     | 0.29 <0.001     | -0.17 <0.01     | 0.10 0.09       | 0.27 <0.001     | 0.03 0.64       |
| Energy intake (kcal/d) | 0.12 <0.05     | 0.10 0.08       | -0.05 0.37      | 0.00 0.95       | 0.02 0.78       | 0.10 0.10       |
| Protein intake (% Energy) | 0.06 0.35     | -0.07 0.25      | 0.03 0.67       | -0.05 0.38      | -0.01 0.91      | 0.04 0.50       |
| Fat intake (% Energy) | 0.08 0.17      | -0.09 0.13      | 0.08 0.16       | -0.03 0.64      | 0.17 <0.01      | 0.09 0.15       |

$^1$High-density lipoprotein.
$^2$Low-density lipoprotein.
$^3$Pearson’s correlation coefficients.
$^4$Body mass index.
| Predictor variables | Serum HDL (mg/dl) | Serum LDL (mg/dl) | Serum HDL (mg/dl) | Serum LDL (mg/dl) |
|---------------------|------------------|-------------------|-------------------|-------------------|
|                     | b (SE) \(^1\)   | \(\beta\) \(^2\) | p                 | b (SE) \(^1\)   | \(\beta\) \(^2\) | p                 |
| Boys (n=287)        |                  |                   |                   |                  |                   |                   |
| Birth weight (kg)   | 3.10 (1.88)      | 0.10              | 0.10              | -1.61 (3.81)     | -0.03             | 0.67              |
| Postmenarcheal age (y) | 0.16 (0.17)  | 0.07              | 0.36              | -0.12 (0.35)     | -0.03             | 0.74              |
| Body weight (kg)    | -0.49 (0.14)     | -0.35             | <0.01             | 0.22 (0.29)      | 0.08              | 0.45              |
| Percent body fat (%) | 0.40 (0.25)    | 0.15              | 0.11              | 1.59 (0.50)      | 0.30              | <0.01             |
| Physical activity (d/wk) | 1.53 (0.30) | 0.34              | <0.001            | -0.81 (0.60)     | -0.09             | 0.18              |
| Energy intake (kcal/d) | 0.00 (0.00)  | 0.05              | 0.39              | 0.00 (0.00)      | -0.01             | 0.94              |
| Protein intake (% Energy) | -0.19 (0.27) | -0.05             | 0.48              | -0.09 (0.55)     | -0.01             | 0.87              |
| Fat intake (% Energy) | -0.02 (0.15) | -0.01             | 0.89              | 0.11 (0.30)      | 0.02              | 0.72              |
|                     | 0.144            | 0.147             |                   |                   |                   |                   |
| Model 2             |                  |                   |                   |                   |                   |                   |
| Birth weight (kg)   | 0.79 (1.82)      | 0.03              | 0.67              | -0.76 (3.58)     | -0.01             | 0.83              |
| Postmenarcheal age (y) | -0.22 (0.16) | -0.09             | 0.15              | 1.87 (0.31)      | 0.35              | <0.001            |
| Percent body fat (%) | -0.42 (0.28)   | -0.26             | <0.001            | -0.65 (0.56)     | -0.07             | 0.24              |
| Physical activity (d/wk) | 1.18 (0.38) | 0.26              | <0.001            | 0.00 (0.00)      | 0.00              | 0.96              |
| Energy intake (kcal/d) | 0.00 (0.00)  | 0.02              | 0.78              | 0.00 (0.00)      | 0.00              | 0.96              |
| Protein intake (% Energy) | -0.23 (0.28) | -0.05             | 0.40              | -0.08 (0.54)     | -0.01             | 0.88              |
| Fat intake (% Energy) | 0.02 (0.15)    | 0.89              | 0.09 (0.30)       | 0.02 (0.75)      | 0.17              | <0.01             |
| R\(^2\)            | 0.096            | 0.145             |                   |                   |                   |                   |
| Girls (n=286)       |                  |                   |                   |                  |                   |                   |
| Birth weight (kg)   | 5.68 (2.19)      | 0.15              | <0.05             | -0.21 (0.58)     | -0.02             | 0.72              |
| Postmenarcheal age (y) | -0.22 (0.20) | -0.09             | 0.27              | -0.22 (0.37)     | -0.10             | 0.24              |
| Body weight (kg)    | -0.36 (0.19)     | -0.20             | 0.06              | -0.01 (0.35)     | -0.00             | 0.98              |
| Percent body fat (%) | -0.20 (0.24)    | -0.01             | 0.93              | 0.65 (0.45)      | 0.14              | 0.15              |
| Physical activity (d/wk) | 1.56 (0.35) | 0.29              | <0.001            | 0.67 (0.64)      | 0.07              | 0.30              |
| Energy intake (kcal/d) | 0.00 (0.00)  | -0.02             | 0.77              | 0.01 (0.00)      | 0.11              | 0.08              |
| Protein intake (% Energy) | -0.07 (0.26) | -0.02             | 0.80              | -0.01 (0.49)     | -0.00             | 0.98              |
| Fat intake (% Energy) | 0.46 (0.16)    | 0.17              | <0.01             | 0.39 (0.30)      | 0.08              | 0.20              |
| R\(^2\)            | 0.169            | 0.059             |                   |                   |                   |                   |

\(^1\)High-density lipoprotein.  
\(^2\)Low-density lipoprotein.  
\(^3\)Multiple regression coefficient (standard error).  
\(^4\)Standardized partial regression coefficient.  
\(^5\)Coefficient of determination.
(b = -0.49, p < 0.01) and a higher frequency of physical activity (b = 1.53, p < 0.001) in model 1, and a higher frequency of physical activity (b = 1.18, p < 0.001) in model 2 individually were significantly associated with greater serum HDL. Also in boys, birth weight had no significant association with serum LDL, while a higher percent body fat (b = 1.59, p < 0.01 in model 1 and b = 1.87, p < 0.001 in model 2) was significantly associated with greater serum LDL. In girls, a higher birth weight (b = 5.68, p < 0.05) was significantly associated with greater serum HDL, while a higher physical activity (b = 1.56, p < 0.001) and fat intake (b = 0.46, p < 0.01) were significantly associated with greater serum LDL in model 2. There was no significant association with serum HDL in model 1. However in girls, birth weight had no significant association with serum LDL, while a lower percent body fat (b = -0.34, p < 0.05) and a higher physical activity (b = 1.28, p < 0.001) and fat intake (b = 0.48, p < 0.01) were significantly associated with greater serum HDL in model 2. There was no significant association with serum LDL in girls in model 1. In model 2, birth weight had no significant association with serum LDL, while a higher percent body fat (b = 0.68, p < 0.05) was significantly associated with greater serum LDL in girls. The results did not change when the subject’s age was added into each model.

**DISCUSSION**

In this study, the relations between birth weight and serum HDL and LDL cholesterol levels were examined in Japanese late adolescents. Birth weight was positively associated only with serum HDL in girls independently of percent body fat and fat intake only when adjusted for current body height and weight. Most of the articles focusing on relationships between birth weight and serum cholesterol levels in later life used current body size as a correction factor (2, 3). However, current body size may have positive correlation with birth weight partly due to genetic effect. In fact, we found positive correlation between birth weight and body height and weight in both sexes in this study. Thus, we employed two types of models with or without body height and weight as predictor variables. In girls, significant correlation between birth weight and serum HDL was detected only when the model using body height and weight was applied: the relationship is still unclear. Another analysis method considering genetic effect would be required for the validation.

Serum lipid levels in adolescents change drastically with changes in sex steroid hormones as they develop (10). Thus, it should be considered that there is a range of serum lipid levels associated with the growing phase in individuals, even those of the same age, especially in early or middle adolescence. However, the relations between serum lipid levels and growing phase are not linear (11); therefore, it is not appropriate to adjust serum lipid levels linearly with the growing phase. Several studies have reported that total and LDL cholesterol levels decreased once during puberty, especially in males (12–14). We actually confirmed that in boys: LDL cholesterol decreased from the 1st to 2nd year of junior high school and thereafter increased in subjects of this study (data not shown). In this study, we analyzed the data in the 3rd year of high school where HDL and LDL cholesterol levels were assumed to be close to adult levels and stable.

In childhood and adolescence, serum low HDL or high LDL was shown to be associated with contemporary atherosclerosis (15). It may also indicate that risk factors such as serum total or LDL cholesterol levels in childhood or adolescence predict the risk associated with adult cardiovascular disease (16, 17). Thus, it may be necessary to examine serum lipid levels at a young age to predict current and future risk of cardiovascular events.

In a previous study of Japanese subjects, birth weight was inversely related to serum total cholesterol, but not to HDL cholesterol, at the middle adolescent age of 15 or 16 in both sexes (18). In another study, higher birth weight was significantly associated with lower serum total cholesterol in both sexes at age 20 (19). Furthermore, birth weight was inversely correlated with serum total cholesterol, but only in males at 22.5 y (20). We could not identify the reasons for the difference of the results among all of these studies, including this study. The differences of subject age and confounding factors may be part of the reason; moreover, we examined serum LDL cholesterol instead of total cholesterol. This may also have affected the differences in the results.

Increase in body fat among children and adolescents was suggested to be associated with adverse changes in serum lipids (4, 5). In this study, percent body fat had a positive association with serum LDL only in boys. Physical activity may also have a positive effect on serum lipids among children (6). In this study, physical activity had a positive association with serum HDL in both sexes.

Currently in Japan, the mean birth weight has been decreasing and the prevalence of low-birth weight infants (birth weight < 2,500 g) has also been increasing, while an opposite trend has been shown in Western countries (21). Takimoto et al. indicated that the increase in preterm deliveries and multiple gestations were important factors with regard to the increase in low-birth weight infants in Japan (21). In addition, a decrease in BMI of young women with childbearing potential may be another important factor (22). Actually, the National Nutrition Survey showed a decreasing trend of BMI among young Japanese women in recent years (23). In this study, lower birth weight at full term and single births may be partly due to the mother’s poor nutrition status.

Our study had several limitations; blood sampling was conducted under nonfasting conditions. However, it is known that the effects of meal intake on serum HDL and LDL cholesterol levels are insignificant (24). We were not able to estimate dietary cholesterol intake with a food frequency questionnaire. In addition, we did not examine the Tanner stage (25) as a growing phase out of consideration for the subjects’ privacy. Thus, only for girls, were we able to verify the effects of growing phase by menarcheal age. Furthermore, we did not assess
dietary or physical activity habits of the subjects at an earlier age.

In conclusion, we found that in healthy Japanese late adolescents, birth weight had a significantly positive effect on serum HDL cholesterol levels independently of physical activity and fat intake in girls when adjusted for current body height and weight, but not in boys. Further studies would be required for the clarification of the relationship between birth size and serum lipids considering genetic effect and also the relationship in younger ages while appropriately adjusting for their growing phase.

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