Research Article

# Birth Weight and Risk Factors for Atherosclerosis: A Retrospective Cohort Study in Japanese Workers

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## Abstract

**Background and aims:** Low birth weight is associated not only with poor birth outcome but also chronic health conditions such as hypertension in later life. B-type natriuretic peptide (BNP) is a prognostic factor of cardiovascular events in the general population. However, the association between birth weight and BNP remains unclear. Here, we examined the relationships among birth weight and risk factors for atherosclerosis, including BNP, in Japanese workers.

**Methods:** A total of 1109 (517 male, 592 female; age 40–70 years) participants in an annual medical checkup were enrolled. Subjects were divided into three groups according to birth weight, and the associations between their birth weight and risk factors for atherosclerosis were examined by statistical analysis.

**Results:** Jonckheere–Terpstra trend test according to birth weight category revealed that although birth weight was not correlated with BNP level, it was inversely associated with HbA1c in men and with diastolic blood pressure in women. Correlation coefficient tests for both categorical and continuous birth weight data confirmed the trend test findings. Multiple regression analysis indicated that birth weight was an explanatory factor for HbA1c in men and for diastolic blood pressure in women.

**Conclusions:** Although no significant association was observed between birth weight and BNP, inverse associations between birth weight and HbA1c in men and diastolic blood pressure in women were found. These findings suggest that birth weight may partially predict future risk of cardiovascular events.

**Keywords:** Birth Weight; Natriuretic Peptide; Blood Pressure; HbA1c

## Introduction

An estimated 15%–20% of all births are diagnosed with low birth weight (birth weight < 2500 g), which is more than 20 million births per year globally [1]. Low birth weight is associated with neonatal morbidity and mortality [1]. In addition, low birth weight is associated with cardiovascular risk factors such as elevated blood pressure [2,3], lowered kidney function [4,5], dysregulation of lipid metabolism [6,7], and impaired glucose homeostasis [8,9] in later life.

B-type natriuretic peptide (BNP) is a hormone secreted mainly by cardiac ventricles [10], and it plays important roles in regulating volume homeostasis [11], cardiac fibrosis [12], vascular remodeling [13], and blood pressure [14]. Because it is increased in response to myocardial stretch and wall tension, plasma BNP is a strong biomarker for the diagnosis [15] and prognosis [16] of congestive heart failure. In a community-based population without heart failure, plasma BNP has been shown to predict risk of death and cardiovascular events [17].

We hypothesized that birth weight could be a useful clinical prognostic factor of plasma BNP level and therefore of cardiovascular events in the general population. However, the literature contains little information on the association between birth weight and plasma natriuretic peptide levels. A previous study has shown that young adults born with very low birth weight (birth weight < 1500 g) have a higher plasma level of N-terminal (NT) pro C-type natriuretic peptide (CNP), which regulates vascular tone and growth, than those born with normal weight; however, no difference in NT-proBNP level was observed [18].

Here, we examined the association between birth weight and risk factors for atherosclerosis, including plasma BNP level, in Japanese workers.

## Patients and Methods

### Study Design and Participants

This study was approved by the Keio University School of Medicine Ethics Committee (Approval No. 2018-0019-2) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

This retrospective cohort study enrolled male and female Japanese workers, aged 40–70, who received an annual medical checkup performed by the Keio University Health Center (Japan) in 2018. Birth weight was obtained as continuous data and/or categorical data (<2500, 2500–2999, 3000–3499, 3500–3999, or >4000 g) via a self-administered questionnaire. Those who did not agree to be enrolled and those who did not complete the examinations or questionnaire were excluded from the study.

## Anthropometric and Biochemical Measurements

Standing height and body weight were measured without shoes and outer clothing. Body mass index (BMI) was calculated as body weight divided by the square of the height ($kg/m^2$).

Blood pressure (BP) was measured by a trained nurse using an electronic sphygmomanometer (BP-103i II; Omron Colin Co., Ltd., Tokyo, Japan) on the right arm in the seated position. When the measured BP was >130/85 mm Hg, the BP was re-measured, and the average of the two measurements was used for the analysis.

Plasma BNP was measured by chemiluminescent enzyme immunoassay. Peripheral blood cells were counted by flow cytometric assay. Total protein and albumin were measured by the Biuret method and the modified bromocresol purple method, respectively. Liver enzymes were assayed by using the Japanese Society of Clinical Chemistry standard method. Serum creatinine and triglycerides (TGs) were measured by enzymatic methods. Both high-density lipoprotein cholesterol (HDLC) and low-density lipoprotein cholesterol (LDLC) were measured by the direct method. Serum uric acid was determined by the uricase/peroxidase method. Fasting blood glucose (FBG) was assayed by ultraviolet absorption spectrophotometry. Hemoglobin A1c (HbA1c) was measured by the agglutination method.

## Outcome Measures

We examined the association between birth weight and risk factors for atherosclerosis. The primary outcome measure was plasma BNP level, and the secondary outcome measures were BMI, BP, creatinine, uric acid, TGs, HDLC, LDLC, FBG and HbA1c.

## Statistical Analyses

Baseline characteristics were summarized as means (SD) for continuous variables and as frequencies (proportions) for categorical variables.

To compare baseline characteristics by birth weight, participants were divided into three groups based on their birth weight (category 1, <2999 g; category 2, 3000–3499 g; category 3, >3500 g). The Jonckheere–Terpstra trend test was used to assess ordered differences among the birth weight categories.

To evaluate the clinical utility of birth weight for determining atherosclerotic risks, variables correlated with birth weight were assessed using a multivariable linear regression model. To avoid multicollinearity among the independent variables, correlation coefficients between pairs of variables were determined. Values were transformed to logarithmic scales when they were not normally distributed but had a log-normal distribution.

All statistical analyses were performed by using SPSS Statistics 25 (IBM Corporation, Armonk, NY). Statistical significance was defined as a *P* value less than 0.05 by using a two-sided test.

## Results

### Characteristics of the Participants

A total of 3384 Japanese workers aged 40–70 attended an annual medical checkup at Keio University Health Center, of which 1180 agreed to be enrolled in the present study. Continuous and/or categorical birth-weight data were available for 1109 of these 1180 participants (94%). The characteristics of the final study cohort are shown in Table 1. The mean age of the cohort was 50.3 years (48.4 years for men and 51.8 years for women), 53.4% of the subjects were female, and 5.0% of the subjects (3.9% of men and 5.9% of women) were diagnosed with low birth weight (<2500 g). Mean plasma BNP was 14.1 pg/μL for men and 22.4 pg/μL for women.

The results of the Jonckheere–Terpstra trend test for the characteristics of the participants according to birth-weight category and sex are shown in Table 2. In men, birth weight was significantly associated with HbA1c, whereas in women, it was significantly associated with diastolic BP and alkaline phosphatase (ALP). BNP level was not significantly associated with birth weight category for either sex.

### Association Between Birth Weight and Risk Factors for Atherosclerosis

Next, we examined the association between birth weight and risk factors for atherosclerosis by using the Pearson correlation coefficient test using continuous birth-weight data ($n$ = 212 for males, 359 for females). In men, birth weight was significantly negatively correlated with FBG (−0.135, 95% CI [−0.270, −0.001]) and HbA1c (−0.217, [−0.350, −0.084]). In women, birth weight was significantly negatively correlated with diastolic BP (−0.091, [−0.195, 0.000]).

The association among birth weight and risk factors for atherosclerosis was also examined by using categorical birth-weight data and Spearman's rank correlation coefficient test ($n$ = 517 for men, 592 for women). Birth weight category was significantly correlated with HbA1c in men (−0.124, [−0.210, −0.038]), and with diastolic BP in women (−0.091, [−0.174, −0.016]).

Log-transformed BNP level was not significantly correlated with birth weight, irrespective of whether continuous or categorical data was used (Pearson correlation coefficient using continuous birth-weight data: −0.006, [−0.130, 0.142] in men and −0.047, [−0.152, 0.057] in women; Spearman's rank correlation coefficient using categorical birth-weight data: −0.030, [−0.116, 0.056] in men and −0.070, [−0.150, 0.011] in women).

### Multiple Linear Regression for the Relationship Between Birth Weight and Risk Factors for Atherosclerosis

A multiple linear regression with HbA1c as the dependent variable was conducted in men. Age, birth weight (continuous data), BMI, systolic BP, white blood cell (WBC), hemoglobin, platelets, log(AST), log(ALT), log(ALP), log(γGTP), creatinine, uric acid, log(TGs), HDLC, LDLC, and log(BNP) were permitted to enter the regression model. HbA1c was significantly correlated with BMI, ALT, birth weight, creatinine, hemoglobin, WBC, and platelets ($R^2$ = 0.278) (Table 3).

A similar multiple linear regression with diastolic BP as the dependent variable was conducted in women. Diastolic BP was significantly correlated with γGTP, BMI, and hemoglobin ($R^2$ = 0.131); however, no correlation was observed with birth weight (Table 4).

## Discussion

Here, we examined the association between birth weight and risk factors for atherosclerosis, especially plasma BNP level, in Japanese workers. We expected to find an association between birth weight and BNP, which is a predictor of cardiovascular events in the healthy general population [17]; however, no association was observed.

In the only study in the current literature in which the association between birth weight and natriuretic peptides was examined [18], plasma NT-proCNP level was higher in young adults diagnosed with very low birth weight (<1500 g) than in those born at normal birth weight, whereas no difference in NT-proBNP level was observed [18], which is consistent with the present results. One explanation for why an association was found between birth weight and CNP, but not NT-proBNP, may be that CNP is produced in response to vascular stress and predicts vascular risks more sensitively than does NT-proBNP [19]. This suggests that it may have been better to examine the association between birth weight and CNP.

In the present study, a sex difference was observed in the association between birth weight and risk factors for atherosclerosis; that is, birth weight was negatively correlated with HbA1c level in men but with diastolic BP in women. Low birth weight is known to be related to the development of impaired glucose tolerance and type 2 diabetes in adulthood [20]. It has been reported from a large population-based study conducted in Australia that the age and sex–adjusted odds ratio for high HbA1c level (>90th percentile) was 0.81 for a 1-kg increase in birth weight, and that an association between birth weight and high HbA1c was seen in the female, but not the male subgroup [21]. Other previous studies have also shown a strong association between low birth weight and adult-onset diabetes in women but not in men [22,23]. These sex differences may be partially explained by greater

survival of females exposed to under-nutrition *in utero* [24] or by sexual dimorphism in susceptibility to develop diabetes [25]. However, in contrast to these previous findings, we found an association between birth weight and HbA1c not in women but in men. Although the reason for this contradictory finding is unknown, race- or ethnicity-based differences in the study participants between our and the previous study cohorts may be an important factor because the prevalence of diabetes mellitus is much lower in Japanese women compared with Western women [26]. Further studies are needed to clarify the underlying cause of these inconsistent findings.

Adult systolic BP has been shown to be inversely related to birth weight [27]. The present study indicated that birth weight was associated with diastolic BP only in the female subgroup. Previous studies have demonstrated that the association between birth weight and adult BP in women was greater than [28] or equal to [29] that in men. BP is affected by cigarette smoking [30,31], alcohol intake [32,33], and obesity [34], which are less common in Japanese women than in men [35], suggesting the possibility of a high influence of birth weight on future blood pressure in women in the present study.

In the present study, we found that birth weight was significantly associated with diastolic, but not systolic, BP. It has been reported that diastolic BP is a more sensitive marker of vascular endothelial dysfunction compared with systolic BP [36,37], and that low birth weight is associated with decreased endothelial progenitor cell numbers and nitric oxide levels [38]. Therefore, it may be that low birth weight is a risk factor for vascular endothelial dysfunction, consequently diastolic BP could be an early marker of endothelial dysfunction.

The present study has some limitations. First, the population was restricted to middle-aged and elderly Japanese workers; therefore, our findings may not be generalizable to younger populations or other ethnicities. Second, 67% of the target population (2275 people) declined to participate in the study or were excluded due to missing data, which may have resulted in selection bias. Third, the study relies on self-reported measures of birth weight. Fourth, the lack of information concerning factors related to BNP levels, such as the levels of other natriuretic peptides, the proportion of smokers and the results of electrocardiography and echocardiography examinations, may have masked the association between birth weight and BNP. Fifth, the population in the present study is healthy enough to work so that the prevalence of atherosclerotic risk factors is low and BNP levels are within almost normal range. This might lead to miss the association of birth weight with atherosclerotic risk factors and with BNP levels. In the future, a prospective study including a different race and using non-self-reported birth weight data will be necessary to further improve our understanding of the association between birth weight and atherosclerotic risk factors.

## Conclusion

In the present study, we found no association between birth weight and plasma BNP level, although an inverse relationship between birth weight and HbA1c in male, and diastolic BP in female, Japanese workers aged 40–70 years was observed. Although this study included some limitations and some findings were inconsistent with those of previous studies, our findings suggest that birth weight may partially predict the future risk factors for atherosclerosis, including BP and HbA1c.

| | Male | | Female | |
|---|---|---|---|---|
| Variable | *n* | | *n* | |
| Age, mean (SD), year | 517 | 48.4 (7.5) | 592 | 51.8 (6.2) |
| Birth weight, mean (SD), g | 212 | 3275 (457) | 359 | 3122 (432) |
| <2999 g, *n* (%) | | 159 (30.8) | | 231 (39.0) |
| 3000–3499 g, *n* (%) | | 242 (46.8) | | 262 (44.3) |
| >3500 g, *n* (%) | | 116 (22.4) | | 99 (16.7) |
| Height, mean (SD), cm | 517 | 171.4 (6.2) | 592 | 158.8 (5.4) |
| Weight, mean (SD), kg | 517 | 69.5 (9.9) | 592 | 54.3 (8.6) |
| BMI, mean (SD), $kg/m^2$ | 517 | 23.7 (3.0) | 592 | 21.5 (3.3) |
| Systolic BP, mean (SD), mm Hg | 517 | 123.6 (15.5) | 592 | 114.9 (16.6) |
| Diastolic BP, mean (SD), mm Hg | 517 | 77.6 (10.6) | 592 | 70.4 (11.3) |
| Hypertension, *n* (%) | | 84 (16.2%) | | 39 (6.6%) |
| Diabetes Mellitus, *n* (%) | | 16 (3.1%) | | 7 (1.2%) |
| WBC, mean (SD), / μL | 517 | 5583 (1458) | 592 | 5578 (1450) |
| RBC, mean (SD), $10^6$/μL | 517 | 489 (44) | 592 | 440 (41) |
| Hemoglobin, mean (SD), g/dL | 517 | 15.0 (1.2) | 592 | 13.1 (1.4) |
| Hematocrit, mean (SD), % | 517 | 45.7 (3.8) | 592 | 40.5 (3.9) |
| Platelets, mean (SD), $10^3$/μL | 517 | 249 (48) | 592 | 266 (61) |
| Total protein, mean (SD), g/dL | 517 | 7.3 (0.5) | 592 | 7.2 (0.5) |
| Albumin, mean (SD), g/dL | 517 | 4.6 (0.3) | 592 | 4.5 (0.3) |
| AST, mean (SD), U/L | 517 | 24.9 (8.9) | 592 | 21.6 (10.3) |
| ALT, mean (SD), U/L | 517 | 26.7 (16.7) | 592 | 17.7 (14.6) |
| ALP, mean (SD), U/L | 517 | 202.3 (54.8) | 592 | 188.2 (62.6) |
| γ-GTP, mean (SD), U/L | 517 | 50.2 (80.5) | 592 | 25.1 (23.7) |
| Creatinine, mean (SD), mg/dL | 517 | 0.90 (0.14) | 592 | 0.65 (0.10) |
| Uric acid, mean (SD), mg/dL | 517 | 6.2 (1.2) | 592 | 4.4 (1.0) |
| Triglycerides, mean (SD), mg/dL | 517 | 121.4 (123.6) | 592 | 82.5 (50.7) |
| HDLC, mean (SD), mg/dL | 517 | 61.7 (15.5) | 592 | 73.5 (16.9) |
| LDLC, mean (SD), mg/dL | 517 | 126.5 (30.4) | 592 | 119.5 (33.4) |
| FBG, mean (SD), mg/dL | 517 | 98.2 (17.5) | 592 | 93.4 (12.9) |
| Hemoglobin A1c, mean (SD), % | 516 | 5.6 (0.5) | 591 | 5.5 (0.4) |
| BNP, mean (SD), pg/μL | 516 | 14.1 (15.9) | 591 | 22.4 (16.1) |

BMI: Body mass index; BP: blood pressure; WBC: white blood cell; RBC: red blood cell; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; FBG: fasting blood glucose; BNP: B-type natriuretic peptide

**Table 1:** Characteristics of the study participants.

| Variable | Male | | | *P* |
|---|---|---|---|---|
| | Category 1 <2999 g (*n* = 159) | Category 2 3000–3499 g (*n* = 242) | Category 3 >3500 g (*n* = 116) | |
| BNP, mean (SD), pg/μL | 15.6 (20.6) | 13.8 (13.7) | 12.9 (12.2) | 0.522 |
| Age, mean (SD), year | 45.4 (5.7) | 54.1 (6.3) | 42.0 (1.4) | 0.092 |
| BMI, mean (SD), $kg/m^2$ | 23.5 (3.1) | 23.6 (2.8) | 23.9 (3.1) | 0.191 |
| Systolic BP, mean (SD), mm Hg | 123.7 (16.0) | 123.3 (15.3) | 124.3 (15.6) | 0.431 |
| Diastolic BP, mean (SD), mm Hg | 77.7 (11.2) | 77.4 (10.0) | 77.8 (11.0) | 0.753 |
| Hypertension, *n* (%) | 33 (20.8%) | 38 (15.7%) | 13 (11.2%) | 0.033 |
| Diabetes Mellitus, *n* (%) | 7 (4.4%) | 5 (2.1%) | 4 (3.4%) | 0.529 |
| WBC, mean (SD), /μL | 5577 (1419) | 5578 (1564) | 5599 (1285) | 0.751 |
| RBC, mean (SD), $10^6$/μL | 492 (42) | 488 (51) | 486 (31) | 0.132 |
| Hemoglobin, mean (SD), g/dL | 15.0 (1.1) | 15.0 (1.4) | 14.9 (0.9) | 0.401 |
| Hematocrit, mean (SD), % | 45.8 (3.4) | 45.7 (4.3) | 45.4 (3.0) | 0.351 |
| Platelets, mean (SD), $10^3$/μL | 239 (46) | 238 (47) | 244 (54) | 0.479 |
| Total protein, mean (SD), g/dL | 7.3 (0.4) | 7.3 (0.6) | 7.3 (0.4) | 0.703 |
| Albumin, mean (SD), g/dL | 4.7 (0.3) | 4.6 (0.4) | 4.6 (0.2) | 0.630 |
| AST, mean (SD), U/L | 25.1 (9.7) | 24.8 (8.6) | 24.6 (8.4) | 0.843 |
| ALT, mean (SD), U/L | 26.9 (16.1) | 27.4 (17.9) | 25.0 (14.8) | 0.391 |
| ALP, mean (SD), U/L | 204.3 (50.2) | 204.0 (57.3) | 196.1 (55.7) | 0.118 |
| γ -GTP, mean (SD), U/L | 50.5 (66.9) | 46.1 (45.8) | 58.2 (135.7) | 0.769 |
| Creatinine, mean (SD), mg/dL | 0.91 (0.15) | 0.89 (0.14) | 0.90 (0.11) | 0.794 |
| Uric acid, mean (SD), mg/dL | 6.2 (1.1) | 6.1 (1.2) | 6.2 (1.2) | 0.567 |
| Triglycerides, mean (SD), mg/dL | 116.3 (70.4) | 128.6 (164.0) | 113.2 (71.5) | 0.500 |
| HDLC, mean (SD), mg/dL | 62.2 (15.1) | 61.2 (16.0) | 62.1 (14.8) | 0.936 |
| LDLC, mean (SD), mg/dL | 128.6 (29.7) | 126.6 (31.8) | 123.6 (28.4) | 0.259 |
| FBG, mean (SD), mg/dL | 99.5 (16.9) | 98.1 (19.7) | 96.7 (12.6) | 0.126 |
| HbA1c, mean (SD), % | 5.6 (0.7) | 5.5 (0.4) | 5.5 (0.4) | 0.009 |

| | Female | | | |
|---|---|---|---|---|
| Variable | Category 1 <2999 g (*n* = 231) | Category 2 3000–3499 g (*n* = 262) | Category 3 >3500 g (*n* = 99) | *P* |
| BNP, mean (SD), pg/μL | 24.1 (17.9) | 21.5 (15.1) | 20.5 (14.0) | 0.071 |
| Age, mean (SD), year | 51.4 (3.6) | 52.9 (7.7) | 49.9 (6.3) | 0.574 |
| BMI, mean (SD), $kg/m^2$ | 21.6 (3.4) | 21.3 (3.1) | 21.8 (3.6) | 0.893 |
| Systolic BP, mean (SD), mm Hg | 116.6 (17.4) | 113.8 (16.4) | 114.0 (15.0) | 0.216 |
| Diastolic BP, mean (SD), mm Hg | 71.7 (11.3) | 69.6 (11.6) | 69.2 (10.2) | 0.027 |
| Hypertension, *n* (%) | 24 (10.4%) | 11 (4.2%) | 4 (4.0%) | 0.006 |
| Diabetes Mellitus, *n* (%) | 4 (1.7%) | 2 (0.8%) | 1 (1.0%) | 0.409 |
| WBC, mean (SD), /μL | 5668 (1461) | 5550 (1567) | 5440 (1405) | 0.185 |
| RBC, mean (SD), $10^6$/μL | 442 (37) | 440 (45) | 437 (40) | 0.375 |
| Hemoglobin, mean (SD), g/dL | 13.0 (1.4) | 13.1 (1.4) | 13.1 (1.4) | 0.580 |
| Hematocrit, mean (SD), % | 40.4 (3.7) | 40.5 (4.1) | 40.5 (3.8) | 0.642 |
| Platelets, mean (SD), $10^3$/μL | 265 (56) | 269 (60) | 263 (73) | 0.555 |
| Total protein, mean (SD), g/dL | 7.3 (0.4) | 7.2 (0.6) | 7.3 (0.4) | 0.943 |
| Albumin, mean (SD), g/dL | 4.5 (0.3) | 4.5 (0.4) | 4.5 (0.2) | 0.338 |
| AST, mean (SD), U/L | 21.6 (9.4) | 21.8 (11.6) | 21.2 (8.8) | 0.652 |
| ALT, mean (SD), U/L | 18.1 (15.0) | 17.7 (15.3) | 16.9 (11.2) | 0.493 |
| ALP, mean (SD), U/L | 196.7 (68.9) | 184.9 (59.9) | 176.8 (51.1) | 0.004 |
| γ -GTP, mean (SD), U/L | 26.5 (25.0) | 23.9 (22.0) | 25.3 (25.2) | 0.141 |
| Creatinine, mean (SD), mg/dL | 0.66 (0.10) | 0.64 (0.10) | 0.66 (0.10) | 0.581 |
| Uric acid, mean (SD), mg/dL | 4.5 (1.0) | 4.4 (1.0) | 4.4 (0.9) | 0.193 |
| Triglycerides, mean (SD), mg/dL | 88.6 (60.7) | 77.5 (40.2) | 81.7 (49.1) | 0.092 |
| HDLC, mean (SD), mg/dL | 72.6 (16.4) | 73.4 (17.1) | 76.1 (17.4) | 0.173 |
| LDLC, mean (SD), mg/dL | 121.1 (32.5) | 118.2 (32.8) | 119.6 (37.2) | 0.286 |
| FBG, mean (SD), mg/dL | 93.7 (10.4) | 93.1 (12.4) | 93.6 (18.3) | 0.081 |
| Hemoglobin A1c, mean (SD), % | 5.5 (0.4) | 5.4 (0.3) | 5.5 (0.5) | 0.116 |

BNP: B-type natriuretic peptide, BMI: Body mass index; BP: blood pressure; WBC: white blood cell; RBC: red blood cell; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; FBG: fasting blood glucose

**Table 2:** Results of the Jonckheere–Terpstra trend test for the characteristics of the participants according to birth-weight category and sex.

| Variable | Standardized regression coefficient | *P* |
|---|---|---|
| BMI | 0.298 | <0.001 |
| log(ALT) | −0.255 | 0.035 |
| Birth weight | −0.232 | <0.001 |
| Creatinine | 0.226 | 0.001 |
| Hemoglobin | −0172 | 0.014 |
| log(AST) | 0.160 | 0.133 |
| WBC | 0.152 | 0.022 |
| Platelets | 0.147 | 0.023 |
| HDLC | −0.110 | 0.165 |
| log(γ -GTP) | 0.058 | 0.455 |
| Systolic BP | −0.033 | 0.623 |
| LDLC | 0.029 | 0.645 |
| Uric acid | 0.023 | 0.721 |
| Age | 0.018 | 0.772 |
| log(ALP) | −0.009 | 0.892 |
| log(triglycerides) | −0.013 | 0.455 |
| log(BNP) | −0.002 | 0.980 |

BMI: Body mass index; WBC: white blood cell; HDLC: high-density lipoprotein cholesterol; BP: blood pressure; BNP: B-type natriuretic peptide

**Table 3:** Results of the multiple linear regression analysis with hemoglobin A1c as the dependent variable in the male participants.

| Variable | Standardized regression coefficient | *P* |
|---|---|---|
| log(γ -GTP) | 0.214 | 0.001 |
| BMI | 0.204 | 0.001 |
| log(ALT) | −0.152 | 0.120 |
| Hemoglobin | 0.129 | 0.027 |
| log(triglycerides) | 0.109 | 0.090 |
| Creatinine | −0.104 | 0.051 |
| Uric acid | 0.098 | 0.083 |
| WBC | −0.096 | 0.083 |
| log(ALP) | 0.094 | 0.095 |
| Birth weight | −0.084 | 0.086 |
| HbA1c | 0.042 | 0.431 |
| Systolic BP | −0.033 | 0.623 |
| log(AST) | 0.033 | 0.716 |
| Platelets | 0.024 | 0.661 |
| log(BNP) | 0.018 | 0.725 |
| LDLC | 0.004 | 0.938 |
| Age | 0.003 | 0.954 |
| HDLC | 0.001 | 0.982 |

BMI: Body mass index; WBC: white blood cell; BP: blood pressure; BNP: B-type natriuretic peptide; LDLC: low-density lipoprotein cholesterol; HDLC: high-density lipoprotein cholesterol

**Table 4:** Results of the multiple linear regression analysis with diastolic blood pressure as the dependent variable in the female participants.

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## Conflicts of Interest

The authors declare no conflicts of interest associated with this manuscript.

## Author Contributions

**Tatsuhiko Azegami:** Conception, Formal analysis, Investigation, Writing – Original Draft, Supervision, Project administration

**Ayano Murai-Takeda:** Supervision

**Yasunori Sato:** Formal analysis, Supervision

**Hiroshi Itoh:** Supervision

**Masaaki Mori:** Supervision, Funding acquisition

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