

# Low Birth Weight Is Associated With Reduced Adiponectin Concentration in Adult

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**PURPOSE:** Low birth weight has been associated with metabolic and vascular diseases, but the precise mechanism is debated. Adiponectin is one of the key molecules in metabolic disease, and a decrease in level precedes the onset of type 2 diabetes and development of atherosclerosis. Our aim is to examine whether low birth weight is associated with adiponectin concentration in adult.

**METHODS:** We conducted a population-based cross-sectional study of 2277 subjects (1661 men and 616 women) aged 35 to 66 years who had their self-reported birth weights and adiponectin concentrations measured as adults.

**RESULTS:** After adjusting for potential confounders, including age, sex, current body mass index (BMI), smoking status, alcohol consumption, and exercise, geometric mean adiponectin levels were 6.63, 6.45, 6.86, 7.05, 6.75, and 7.22  $\mu\text{g/mL}$  for subjects with birth weights less than 2500, 2500 to less than 2800, 2800 to less than 3000, 3000 to less than 3200, 3200 to less than 3500, and greater than 3500 g, respectively. A positive association was found between birth weight and adiponectin concentration (trend  $p = 0.002$ ). Stratified by current BMI of 25  $\text{kg/m}^2$ , a positive association was not observed for subjects with a BMI less than 25  $\text{kg/m}^2$ , but was pronounced in those with a BMI of 25  $\text{kg/m}^2$  or greater.

**CONCLUSION:** This study indicates that low birth weight contributes to decreased adiponectin concentrations in adult life independently of current BMI, especially for obese subjects.

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**KEY WORDS:** Birth Weight, Adiponectin, Adulthood, Cross-Sectional Study, Japanese.

## INTRODUCTION

During the past decade, there has been sustained interest in the possible role of intrauterine development in the later development of chronic and metabolic disorders. Several epidemiologic studies showed that low birth weight is a risk factor for insulin resistance–based disorders later in life, such as high blood pressure, glucose intolerance, dyslipidemia, and cardiovascular disease (1–6). The precise mechanisms underlying the association between birth weight and these conditions remain unclear. The hypothesis that intrauterine environmental insults at a critical period lead to

permanent changes in the metabolism and structure of fetal organs is proposed as the biologic mechanism explaining these findings.

Adipose tissue expresses a variety of secretory proteins of importance to the contraction of metabolic and vascular disease. Adiponectin is an adipocyte-derived plasma protein of 244 amino acids that recently was discovered (7–10). It is a member of the growing group of adipose-secreted proteins, sometimes described as adipocytokines. Unlike other members in this group, such as leptin and interleukin 6, paradoxically, circulating adiponectin concentration, despite being derived solely from adipose tissue in humans, correlates inversely with body weight and amount of body fat (11, 12). This inverse correlation was suggested to be related to the origin of insulin resistance in obese subjects. Administration of adiponectin to normal or obese mice improved glucose tolerance and insulin sensitivity (13–15).

Interestingly, a recent study of newborns reported a positive association between birth weight and plasma adiponectin level (16), which is completely opposite to the association in adults. Currently, data examining the association of birth weight with adiponectin concentration in adults are lacking. In light of the foregoing observations, we hypothesize that low birth weight may be an additional factor contributing to decreased adiponectin concentrations in adults. Our study provides new information on the

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**Selected Abbreviation and Acronym**

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BMI = body mass index

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mechanism underlying the association between birth weight and metabolic disorders later in life.

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## METHODS

### Study Population

We studied a population of 3814 Japanese (2968 men and 846 women) aged 35 to 66 years belonging to a public office (public servant) in Aichi Prefecture, Japan, who responded to a self-reported questionnaire that included medical history and lifestyle characteristics, underwent a physical examination that included height and weight, and provided fasting blood samples in 2002. All subjects in the study gave their informed consent to the use of personal information for analysis. This study protocol was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine, Nagoya, Japan.

### Assessment of Birth Weight

On the 2002 questionnaire, subjects were asked to indicate their birth weights from the following categories of responses: less than 2500, 2500 to less than 2800, 2800 to less than 3000, 3000 to less than 3200, 3200 to less than 3500, 3500 to less than 4000, and 4000 and greater grams and unknown. Of 3814 subjects, 2277 (59.7%; 1661 men and 616 women) provided the required information on birth weight.

### Assay of Serum Adiponectin Concentration

The 3814 venous blood samples collected were after 8 hours or overnight fasting, and samples were stored at  $-80^{\circ}\text{C}$  until assay. Serum adiponectin concentration was determined by means of an enzyme-linked immunosorbent assay using an enzyme-linked immunosorbent assay kit with a coefficient of variation between 6.0% and 8.6% (Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan). This kit can detect total adiponectin, but not its isoforms. The current analysis ultimately was restricted to 2277 subjects with complete data for birth weight and serum adiponectin concentration.

### Statistical Analysis

The significance of a difference in sex distribution between the 2277 study subjects (birth weight available) and 1537 subjects lacking data for birth weight was assessed by using chi-square test, whereas that for age was analyzed by using Student *t*-test. Because significant differences in both sex and age were observed, comparisons between the two

subject groups were performed by using analysis for covariance, controlled by sex and age, for continuous variables. Serum adiponectin concentrations were skewed and were normalized by means of logarithmic transformation in all analyses. Geometric mean and mean  $\pm$  SE were computed on the log-transformed adiponectin and converted to the original scale of measurement. For categorical variables, covariate-adjusted prevalence rates were calculated from logistic regression models by using covariance adjustment of rates to the mean by a covariate in the sample (17).

One-way analysis of covariance with polynomial contrast in an SPSS statistical package (SPSS Inc., Chicago, IL) was used to evaluate statistical differences and trends in body mass index (BMI) and serum adiponectin concentration across birth-weight categories. Polynomial contrast subcommand estimated linear trends across all birth-weight categories. Because the number of subjects in the birth-weight category of 4000 g or greater was small ( $n = 30$ ), the two categories of 3500 to less than 4000 and 4000 and greater were combined, and mean BMI and serum adiponectin values adjusted by birth weight were estimated in three models: model 1, adjusted for sex and age; model 2, as in model 1 plus BMI (continuous); and model 3, as in model 2 plus smoking status (never, former, and current: dummy variables), frequency of alcohol consumption per week (continuous), and regular exercise ( $\geq 1$  d/wk and  $\geq 60$  min/mo: yes or no).

Multiple linear regression analysis was performed to estimate the contribution of individual variables to serum adiponectin concentration. Log-transformed adiponectin concentrations were dependent variables, whereas independent variables included birth weight (continuous, with 2.3 kg for the lowest category, 4.2 kg for the highest category, and the midpoints of the other categories), sex, age, BMI (continuous), smoking status (never, former, and current: dummy variables), frequency of alcohol consumption per week (continuous), and regular exercise (yes or no). For all linear regression estimates, 95% confidence intervals were calculated.

To elucidate differences and similarities in effects of birth weight according to BMI, subjects were stratified into two subgroups by BMI of  $25 \text{ kg/m}^2$  according to criteria recommended by the Japan Society for the Study of Obesity (18). In addition, we performed the same analysis as mentioned previously.

All analyses were performed using the SPSS 11.0 statistical package.  $p < 0.05$  is considered statistically significant.

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## RESULTS

Distribution of adiponectin concentrations for the present study subjects is shown in Figure 1. Median value is  $6.7 \text{ }\mu\text{g/mL}$ , and range is 0.6 to  $30.4 \text{ }\mu\text{g/mL}$ . Characteristics

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