High circulating adiponectin levels predict decreased muscle strength among older adults aged 70 years and over: a prospective cohort study

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1 **ABSTRACT**

2 **Background and Aims:** Population-based researches indicate that circulating adiponectin is
3 inversely associated with muscle strength. However, interpretation of the findings has been
4 limited by the use of a cross-sectional design. This study aimed to examine the prospective
5 relationship between baseline circulating adiponectin concentration and change in muscular
6 function-related physical performance in older adults.

7 **Methods and Results:** A 1-year prospective cohort study of Japanese community-dwelling
8 elderly was conducted between 2002 and 2003. Four hundred thirty-four older persons
9 participated in the measurements of physical function, including leg extension power,
10 functional reach, timed up-and-go test, and 10-m maximum walking speed, at baseline and
11 follow-up. After adjustment for potential covariates, higher serum adiponectin concentration
12 was found to be significantly associated with poorer physical performance at baseline (leg
13 extension power [watt], $P < 0.001$; functional reach [cm], $P < 0.001$; log timed up-and-go test,
14 $P = 0.007$; log 10-m maximum walking speed, $P < 0.001$). The results of the prospective
15 analysis by analysis of covariance indicated that the elderly with higher serum adiponectin
16 concentrations (tertiles) at baseline tended to have a decreased performance in [leg extension](#)
17 [power \(means \[95% confidence interval\]: lowest, \$-105 \[-125, -85.7\]\$; middle, \$-117 \[-135,\$
18 \$-97.8\]\$; highest, \$-140 \[-160, -120\]\$, watt, \$P\$ for trend = 0.021\)](#) and timed up-and-go test (lowest,
19 $-0.08 [-0.28, -0.12]$; middle, $-0.10 [-0.29, 0.10]$; highest, $0.28 [0.07, 0.48]$, s, P for trend =

20 0.019), but not two other functioning.

21 **Conclusion:** High circulating adiponectin concentration may be an indicator of decreased
22 physical performance, especially muscle strength, in older adults.

23

24 **Keywords:** adipokine; sarcopenia; physical function; aging

INTRODUCTION

Adiponectin, first identified in 1996, is a 244-amino acid protein that is abundantly expressed in adipose tissue [1]. Having been shown to be related to lower incidence rates of type 2 diabetes and metabolic syndrome [2], this adipocyte-derived hormone is believed to benefit human health. Recently, however, increasing evidence from population-based studies indicates that circulating adiponectin level is related to cardiovascular events and mortality in older subjects [3,4]. High circulating adiponectin concentration was also reported to be a predictor of bone mineral density loss [5] and lung function decline [6]. Such epidemiological findings indicate the potentially paradoxical involvement of adiponectin in health status.

Most recently, a population-based epidemiological study showed that the elderly with relatively higher circulating adiponectin levels tended to have an increasing number of frailty components compared to the elderly with relatively lower levels [7]. Furthermore, the potential negative effect of adiponectin on physical function is supported by the findings of two population-based prospective cohort studies that concur that relatively higher serum adiponectin concentration contributes to incident physical disability in older subjects from the United States [8] and Japan [9]. Based on these findings, an inverse correlation between adiponectin and skeletal muscle function, an essential component of physical function, has been hypothesized. Muscle strength decreased after the age of 50 and muscle strength loss is most dramatic after 70 years old [10]. Evidence showed that the lower-extremity muscle

strength in older adults aged 75 years decreased by 16.5% during 2.8 years follow-up [11].
Thus, decline of muscle strength with age become a major public health problem since lower
muscle strength is a predictor of mortality in the elderly [12].

In a previous study, we identified an inverse association between serum adiponectin
concentration and upper- and lower-extremity muscle strength in middle-aged Japanese adults
[13]. Similar findings were reported by several other cross-sectional studies in which high
circulating adiponectin concentration was found to be associated with poor muscle strength in
European adolescents [14] and adults [15,16]. Although an inverse association between
adiponectin concentration and muscle strength has been indicated, prospective research on this
topic is limited. Therefore, this prospective cohort study aimed to examine the relationship
between baseline serum adiponectin concentrations and changes in lower-extremity muscle
strength, as well as other components of physical function among community-dwelling elderly
adults.

SUBJECTS AND METHODS

Study participants

The study participants were the participants of the Tsurugaya Project, a community-based Comprehensive Geriatric Assessment (CGA) of Japanese aged ≥ 70 years who are living in the Tsurugaya area of Sendai City, Japan. In brief, the CGA used a structured approach to measure the physical, mental, and social functionings of older individuals to assess early deterioration in long-term care conditions and promote healthy aging. The methods used in the Tsurugaya Project have been reported in detail elsewhere [9,17].

Among the 2,730 elderly inhabitants residing in the Tsurugaya area in 2002, 1,198 participated in the health survey, yielding a 43.8% response rate, and 1,177 provided written informed consent to be included in the analysis, yielding a 43.1% participation rate. Of the 1,177 potential participants, 672 were excluded from the analysis owing to missing data regarding serum adiponectin concentration and 21 were excluded owing to lack of data regarding physical function measurements, yielding a sample of 484 potential participants at baseline. A further 50 participants were excluded because they had not participated in physical function measurement in 2003 or had a measured value of 0 for leg extension power assessment, which was considered as a measurement error. As a result, an analytical sample of 434 participants was used for the prospective research. The study protocol was approved by the institutional review board of Tohoku University Graduate School of Medicine.

Serum adiponectin measurement

In this study, all blood samples were obtained under nonfasting conditions. It is has been that circulating adiponectin did not differ between fasting and nonfasting conditions [18]. Serum adiponectin concentration was determined by enzyme-linked immunosorbent assay (Otsuka Pharmaceutical, Tokyo, Japan) or latex particle-enhanced turbidimetric immunoassay (Mitsubishi Chemical Medience, Tokyo, Japan), the results of which were closely correlated ($r = 0.98$) [19]. The intra-assay and inter-assay coefficients of variation were $<10\%$ for enzyme-linked immunosorbent assay, and $\leq 2\%$ for latex particle -enhanced turbidimetric immunoassay. All assays were performed at a clinical testing laboratory (SRL, Tokyo, Japan).

Physical function measurement

To assess skeletal muscle strength, maximal bilateral leg extension power was measured using a dynamometer (Anaeropress 3500; Combi Co., Tokyo, Japan). After the subjects sat back on the seat and placed both feet on the sliding footplate with the knee angle adjusted to 90° , a belt was firmly fastened at the waist and the load of the footplate was set to their weight. The subjects were then instructed to extend their legs as much as possible. Five trials were conducted with 15-s intervals between them, and the average value of the two best measurements (farthest extensions) was recorded as the leg extension power (watt). The validity of the leg extension power measurement are described in detail elsewhere [20]. To

assess functional reach, a measure of balance as assessed by measuring the maximal distance that one can reach forward beyond arm's length while standing without losing balance [21], the subjects were asked to place their feet comfortably apart (approximately shoulder width), hold their arms out straight at shoulder height, and then reach as forward as possible while simultaneously maintaining a fixed support in a standing position. The farthest reach in three trials was recorded as functional reach (cm) for statistical analysis. To perform the timed up-and-go test, which assesses mobility [22], the subjects were required to rise from a 46-cm-high armchair, walk 3 m, turn around, return to the chair, and sit down while the time taken to complete the trial was measured with a stopwatch. The test was repeated three times, and the best measurement (fastest time) was recorded for analysis. To perform the 10-m maximum walking speed test, which was used to assess walking ability, the subjects were instructed to walk 10 m as quickly and safely as possible without running while the time taken to complete the trial was recorded by a stopwatch. The test was repeated three times, and the best measurement (fastest time) was recorded and used to calculate maximal walking speed (m/s) [23].

Relevant covariates

Participant sociodemographic data were collected by administration of a questionnaire containing items regarding sex, age, educational level, marital status, and living status.

Anthropometric factors (weight and height) were measured using standard protocols. Body mass index (BMI) was calculated for each individual according to the equation, $\text{BMI} = \text{weight (kg)} / \text{height}^2 (\text{m}^2)$. Based on the classification proposed by the World Health Organization [24], BMI was categorized as <21.0 , $21.0-24.9$, and ≥ 25.0 for analysis in this study. The lifestyle-related covariates of smoking status, drinking status, and physical activity intensity (based on the frequency and duration of physical activity in the past year) [17] were assessed via a self-reported single-item questionnaire.

The health status-related covariates assessed included serum nonfasting glucose concentration, which was measured using enzymatic methods (Shino-Test, Tokyo, Japan) to identify diabetes, defined as a casual blood glucose level ≥ 200 mg/dL or a history of diabetes.

Hyperlipidemia was defined as a serum total cholesterol concentration ≥ 220 mg/dL, triglyceride level ≥ 150 mg/dL, or history of hyperlipidemia. Total serum cholesterol and triglyceride levels were measured using appropriate enzymatic methods (Denka Seiken and Kyowa Medex, Tokyo, Japan, respectively). Chronic kidney disease was defined as an estimated glomerular filtration rate ≤ 60 mL/min/1.73 m², as calculated using a new Japanese equation [25], or a history of chronic kidney disease. Serum high-sensitive C-reactive protein (hsCRP) concentration was measured using an immunotechnique in which the Behring BN II analyzer (Dade Behring, Tokyo, Japan) was used as an inflammatory marker. Albumin level, an indicator of nutritional status, was measured using the bromocresol green method. A serum

albumin level ≤ 3.8 g/dL was considered low. Data regarding history of cardiovascular diseases (CVD) were collected via administration of a self-report questionnaire. Depression was assessed by administration of the 30-item Geriatric Depression Scale (GDS) in Japanese [26], and depressive symptoms were considered present if the GDS score was ≥ 14 [27]. Cognitive function was assessed using the Mini-Mental State Examination (MMSE), and cognitive impairment was considered present if the MMSE score was < 24 [28]. Medications data, including diabetes, lipid-lowering, and antihypertensive drugs, were confirmed by a well-trained pharmacist.

Statistical analysis

Data were analyzed using the IBM SPSS Statistics 19.0 software (IBM SPSS Inc., Chicago, IL, USA). The baseline serum adiponectin concentrations, timed up-and-go test, and 10-m maximum walking speed test were log-transformed due to their skewed distribution of raw data.

The chi-square test for trend was performed to assess the participants' characteristics according to sex-specific tertiles of serum adiponectin concentrations. Data were summarized in terms of as percentage. Univariate and multivariate association of serum adiponectin with each physical function component at baseline or follow-up was examined by linear regression analysis. In multivariate model, a number of potential confounding factors were adjusted,

including baseline physical function (for follow-up analysis only), sex, age (70–74, 75–79, or ≥ 80 years), BMI (<21.0 , $21.0\text{--}24.9$, or ≥ 25.0 kg/m²), marital status (married, widowed or divorced, or never married), living status (living alone), education level (>12 years), depressive symptoms, cognitive impairment, serum albumin level ≤ 3.8 g/dL), serum high-sensitivity CRP level (<1.0 , $1.0\text{--}2.9$, or ≥ 3.0 mg/L), diabetes, hyperlipidemia, chronic kidney disease, history of CVD, number of medications used (diabetes, lipid-lowering, and antihypertensive drugs), smoking status (current, former, or never), drinking status (current, former, or never), and physical activity intensity (low, middle, or high) as assessed at baseline. The results of the multivariate linear regression analysis were expressed as unstandardized regression coefficients (B) and its 95% confidence interval (CI) and β . In addition, a secondary analysis was performed to examine the relationship between sex-specific tertiles of baseline serum adiponectin concentration and 1-year absolute changes in physical functions by using analysis of covariance (ANCOVA). [The covariates used in ANCOVA were the same as those used in the multivariate linear regression model.](#) Results of ANCOVA were summarized as mean and 95% CI. The interactions between serum adiponectin concentration and the confounding factors of physical function were tested by the addition of cross-product terms to the multivariate linear regression model. A *P* value less than 0.05 was considered statistically significant in all the two-sided tests.

RESULTS

Participant characteristics

The participants' baseline characteristics are shown in **Supplemental Table S1**. The mean (SD) age of the population at baseline was 74.5 (4.1) years and 207 participants (47.7%) were female. The mean serum adiponectin concentration in the women was 14.7 mg/L, which was higher than the 10.8 mg/L in the men ($P < 0.001$). In addition, the male elderly had better physical performances than the female elderly at baseline (data not shown). The participants' characteristics according to sex-specific tertiles of serum adiponectin concentration at baseline (**Table 1**) indicated that age, prevalence of depressive symptoms and chronic kidney disease were positively associated with serum adiponectin levels ($P < 0.05$). Conversely, sex-specific serum adiponectin tertiles were found to be inversely associated with BMI, hsCRP, prevalence of hyperlipidemia and diabetes, and medications use ($P < 0.05$). [Further, adiponectin was also associated with poor physical performance \(\$P < 0.05\$ \).](#) No significant associations were found between sex-specific serum adiponectin tertiles and other variables. **Table 2** showed the information on 1-year change in physical function, in which leg extension power decreased most drastically.

Association between serum adiponectin level and physical function

At baseline, multivariate linear regression analysis revealed an inverse association between log

adiponectin and physical performances ($P < 0.01$) (**Table 3**). The results of the prospective analysis indicated that higher baseline log adiponectin was shown to be associated with decreased performance of leg extension power and timed up-and-go test in the full-adjusted model ($P = 0.006$, and $P = 0.047$, respectively) (**Table 4**). Also, ANCOVA showed that declined performance (mean [95% CI]) of leg extension power and timed up-and-go test were higher across the tertiles of baseline serum adiponectin (leg extension power: lowest, $-105 [-125, -85.7]$; middle, $-117 [-135, -97.8]$; highest, $-140 [-160, -120]$, watt, P for trend = 0.021 ; timed up-and-go test: lowest, $-0.08 [-0.28, -0.12]$; middle, $-0.10 [-0.29, 0.10]$; highest, $0.28 [0.07, 0.48]$, s, P for trend = 0.019) (**Figure 1**). Adiponectin was also inversely and significantly associated with leg extension power relative to body weight in a secondary analysis (data not shown). No significant interactions were found between serum adiponectin levels and confounding factors (data not shown).

DISCUSSION

This population-based prospective cohort study was the first to demonstrate that high circulating adiponectin concentration predicts muscle strength decline in community-dwelling elderly, independent of socio-demographic, lifestyle, and health status-related factors.

The findings of this study confirm the well-established cross-sectional association between high circulating adiponectin concentration and poor muscle strength. We recently reported a similar finding from a cross-sectional study in which we found serum adiponectin level to be significantly inversely associated with grip strength and leg extension power in healthy Japanese adults aged 19–83 years, independent of several important potential confounders, including age, BMI, physical activity, serum CRP level, and metabolic syndrome [13]. Over the past few years, this inverse association between circulating adiponectin level and muscle strength has been reported by other cross-sectional studies of age groups ranging from adolescents to the elderly [14–16]. The findings of the present study largely extend these findings by using a prospective cohort design and raise the possibility that adiponectin concentration may be a useful marker in the prediction of muscle strength decline among older people.

Although the reasons for the relationship between high circulating adiponectin concentration and decreased lower-extremity muscle strength could not be explained by the results of the present study, two possible explanations can be hypothesized. First, an

experimental study reported that adiponectin is expressed in skeletal muscle, and an increased type IIB fiber area has been found in adiponectin knockout mice [29]. Confirming this relationship between adiponectin and skeletal muscle morphology, an epidemiological study of 461 older men aged 71 years that found that adiponectin concentration is associated with a lower proportion of type IIB muscle fibers [30]. Considering the positive impact of type II muscle fiber size on muscle strength [31], adiponectin-induced decreased proportion of type IIB muscle fibers possibly mediates the relationship between adiponectin concentration and muscle strength decline observed in this study. More studies are needed to confirm this hypothesis. The second hypothesis is that high adiponectin level in the elderly may not directly affect muscle strength but simply serves as a marker of poor prognosis. It is well-known that muscle strength loss was a useful indicator of malnutrition [32]. Also, high levels of circulating adiponectin may reflect poor nutrition status because adiponectin has been correlated with low muscle mass [16] and circulating albumin levels [8]. Moreover, evidence indicated that adiponectin predicts incidence of CVD in older people [3,4]. According to these considerations, it seems that poor nutrition status and cardiovascular function may mediate the observed association, although the relationship between adiponectin and decline in lower-extremity muscle strength was independent of serum albumin and history of CVD in this study.

It is important to emphasize that high serum adiponectin concentration was found to be associated with poor performances in the functional reach and 10-m maximum walking speed

at baseline, but not at follow-up. Considering the measurement of these physical functions differs from that of leg extension power, because it includes not only measurement of skeletal muscle strength but also balance, flexibility, agility, and/or functional mobility, it is hypothesized that the effect of adiponectin concentration on physical function may be limited to effects on skeletal muscle strength, and not to other components of physical performance. Therefore, more attention should be paid to the potential risk of adiponectin in muscular function and other aspects of human health to know more about this adipocyte-derived hormone, as the findings of this study contribute to the knowledge base regarding the risk factors associated with decreased muscle strength with aging.

Several limitations of the present study should be considered when reviewing the findings. First, despite controlling for many confounders in the multivariate model, other potential confounders may be associated with adiponectin and muscle strength but were not evaluated, such as muscle morphology, muscle mass, or other body compositions. Second, the causality and underlying mechanisms of the relationship between circulating adiponectin and muscle strength could not be identified because of the use of an observational study design. Third, the use of a relatively small sample size did not permit the performance of a stratified analysis. Fourth, serum samples were obtained under nonfasting conditions, which might have increased the possibility of misclassification of some blood parameters. Finally, a longer follow-up duration is desirable, although a 1-year period seems to be sufficient to detect

258 significant changes in lower-extremity muscle strength in the elderly aged 70 years in this
259 study.

260 In conclusion, the results of this first prospective cohort study of the relationship between
261 serum adiponectin concentration and functional performance indicate that high baseline
262 adiponectin concentration is correlated with decreased lower-extremity muscle strength, even
263 after adjustments for a number of potentially confounding factors, in Japanese aged ≥ 70 years.
264 Long-term prospective studies are warranted to confirm and further clarify the relationship
265 between adiponectin concentration and skeletal muscular function.

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FIGURE CAPTIONS

Figure 1. Analysis of covariance on relationship of baseline serum adiponectin concentration tertiles with 1-year absolute change in physical function. Data were shown as means and 95% confidence interval. Participants in each sex-specific tertile of serum adiponectin was 144 (female, 68), 146 (female, 69), and 144 (female, 70), respectively. Covariates include baseline physical function (leg extension power, functional reach, timed up-and-go test, or 10-m maximum walking speed was adjusted as appropriate), sex, age (70–74, 75–79, ≥ 80 years), body mass index (<21.0 , $21.0\text{--}24.9$, ≥ 25.0 kg/m²), marital status (married, widowed or divorced, or never married), living status (living alone), education level (>12 years), smoking status (current, former, or never), drinking status (current, former, or never), physical activity intensity (low, middle, or high intensity), depressive symptoms, cognitive impairment, serum albumin ≤ 3.8 g/dL), high -sensitivity C-reactive protein (<1.0 , $1.0\text{--}2.9$, ≥ 3.0 mg/L), diabetes, hyperlipidemia, chronic kidney disease, history of cardiovascular disease, and the number of medications use (diabetes, lipid-lowering, and antihypertensive drugs).

Table 1 Baseline participants' characteristics according to sex-specific tertiles of serum adiponectin concentration (n = 434)

Variables	Tertiles of adiponectin			<i>P</i> value ^a
	144 (women, 68)	146 (women , 69)	144 (women , 70)	
Adiponectin range, mg/L	Men: <7.8 Women: <10.2	Men: 7.9–11.9 Women: 10.3–16.5	Men: >12.0 Women: >16.6	
Age, years				
70–74, %	74.3	59.6	41.0	
75–79, %	18.1	28.8	42.4	
≥80, %	7.6	11.6	16.7	<0.001
BMI, kg/m ²				
<21, %	8.3	11.0	31.9	
21–24.9, %	46.5	47.9	49.3	
≥25, %	45.1	41.1	18.8	<0.001
Educational level (>12 y), %	37.5	33.6	43.1	0.33
Marital status				
Married, %	72.2	72.6	59.7	
Widowed or divorced, %	25.7	24.0	35.4	
Never married, %	2.1	2.7	3.5	0.08
Living alone, %	19.4	18.5	21.5	0.66
Smoking status				
Current, %	11.8	19.2	8.3	
Former, %	40.3	28.8	33.3	
Never, %	46.5	50.7	55.6	0.29
Drinking status				
Current, %	47.9	52.1	42.4	
Former, %	10.4	8.2	13.9	
Never, %	39.6	36.3	37.5	0.68
Physical activity engagement				
Low intensity, %	30.6	41.8	32.6	
Middle intensity, %	27.8	26.0	34.7	
High intensity, %	27.8	23.3	22.9	0.90
Serum albumin ≤ 3.8 g/dL, %	0.0	5.5	2.1	0.26
High-sensitivity CRP, mg/L				
<1.0, %	61.8	72.6	77.1	
1.0–2.9, %	27.8	19.2	16.7	
≥3.0, %	10.4	8.2	6.3	<0.01

Hyperlipidemia, %	77.1	67.8	54.2	<0.001
Diabetes, %	20.6	15.6	9.8	0.04
Chronic kidney disease, %	25.7	34.2	36.8	0.04
History of CVD, %	15.3	12.3	11.1	0.29
Cognitive impairment, %	3.5	4.1	2.8	0.75
Depressive symptoms, %	6.9	12.3	15.3	0.03
Medications use, %	56.3	49.3	36.8	<0.001
Physical performance				
Leg extension power, watt	737 (693–782)	682 (638–726)	612 (568–657)	<0.001
Functional reach, cm	32.6 (31.8–33.4)	32.6 (31.8–33.5)	29.8 (29.0–30.7)	<0.001
Timed up-and-go test, s	8.6 (8.4–8.8)	8.5 (8.3–8.7)	9.0 (8.8–9.3)	0.014
10-m maximum walking speed, m/s	1.83 (1.78–1.88)	1.81 (1.76–1.86)	1.73 (1.68–1.77)	0.003

^a Differences were determined by chi-square test for trend.

BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease.

Table 2 Information on physical function at baseline and follow-up (n = 434)

	Baseline	Follow-up	Absolute change
Leg extension power, watt	677 (275)	557 (263)	−121 (123)
Functional reach, cm	31.7 (5.2)	29.8 (5.3)	−1.94 (4.56)
Timed up-and-go test, s	8.8 (1.5)	8.9 (1.6)	0.33 (1.25)
10-m maximum walking speed, m/s	1.8 (0.3)	1.8 (0.3)	0.01 (0.21)

Values were expressed as mean (standard deviation).

Table 3 Univariate and multivariate linear regression analysis of the association between serum adiponectin concentration and physical function at baseline (n = 434)

	Log serum adiponectin concentration ^a			
	B (95% CI)	β	R ²	P value
Leg extension power, watt				
Crude model	−221 (−269, −172)	−0.40	0.16	<0.001
Adjusted model ^b	−86.3 (−125, −42.7)	−0.16	0.60	<0.001
Functional reach, cm				
Crude model	−2.75 (−3.71, −1.78)	−0.26	0.07	<0.001
Adjusted model	−1.85 (−2.87, −0.83)	−0.18	0.24	<0.001
Log timed up-and-go test ^a				
Crude model	0.05 (0.02, 0.08)	0.16	0.02	0.001
Adjusted model	0.05 (0.01, 0.08)	0.14	0.16	0.007
Log 10-m maximum walking speed ^a				
Crude model	−0.09 (−0.12, −0.06)	−0.26	0.07	<0.001
Adjusted model	−0.06 (−0.09, −0.03)	−0.16	0.32	<0.001

^a Variable was log-transformed due to its skewed distribution.

^b Adjusted for sex, age (70–74, 75–79, ≥80 years), body mass index (<21.0, 21.0–24.9, ≥25.0 kg/m²), marital status (married, widowed or divorced, or never married), living status (living alone), education level (>12 years), smoking status (current, former, or never), drinking status (current, former, or never), physical activity intensity (low, middle, or high intensity), depressive symptoms, cognitive impairment, serum albumin (≤ 3.8 g/dL), high-sensitivity C-reactive protein (<1.0, 1.0–2.9, ≥3.0 mg/L), diabetes, hyperlipidemia, chronic kidney disease, history of cardiovascular disease, and the number of medications use (diabetes, lipid-lowering, and antihypertensive drugs).

CI, confidence interval.

Table 4 Multivariate linear regression analysis of the relationship between baseline serum adiponectin concentration and 1-year absolute changes in physical function (n = 434)

	Log serum adiponectin concentration ^a			
	B (95% CI)	β	R ²	P value
Leg extension power, watt				
Model 1 ^b	−25.7 (−49.9, −1.47)	−0.10	0.11	0.038
Model 2 ^c	−36.1 (−61.8, −10.4)	−0.15	0.17	0.006
Functional reach, cm				
Model 1	−0.60 (−1.42, 0.22)	−0.06	0.18	0.15
Model 2	−0.19 (−1.11, 0.74)	−0.02	0.22	0.69
Timed up-and-go test, s				
Model 1	0.40 (0.17, 0.62)	0.16	0.15	0.001
Model 2	0.26 (0.00, 0.52)	0.10	0.17	0.047
10-m maximum walking speed, m/s				
Model 1	−0.03 (−0.07, 0.13)	−0.06	0.10	0.19
Model 2	−0.02 (−0.06, 0.03)	−0.04	0.12	0.50

^a Variable was log-transformed due to its skewed distribution.

^b Adjusted for baseline physical function (leg extension power, functional reach, timed up-and-go test, or 10-m maximum walking speed was adjusted as appropriate).

^c Adjusted for model 1 + baseline sex, age (70–74, 75–79, ≥80 years), body mass index (<21.0, 21.0–24.9, ≥25.0 kg/m²), marital status (married, widowed or divorced, or never married), living status (living alone), education level (>12 years), smoking status (current, former, or never), drinking status (current, former, or never), physical activity intensity (low, middle, or high intensity), depressive symptoms, cognitive impairment, serum albumin ≤ 3.8 g/dL, high-sensitivity C-reactive protein (<1.0, 1.0–2.9, ≥3.0 mg/L), diabetes, hyperlipidemia, chronic kidney disease, history of cardiovascular disease, and the number of medications use (diabetes, lipid-lowering, and antihypertensive drugs). CI, confidence interval.

Figure 1