Intensity-Specific and Modified Effects of Physical Activity on Serum Adiponectin in a Middle-Aged Population

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Context: The effects of intensity-specific physical activity (PA) and its interaction with other lifestyle factors on serum adiponectin are currently unclear.

Objective: To investigate the effects of replacing sedentary time with either light-intensity PA (LPA) or moderate- to vigorous-intensity PA (MVPA) on total and high-molecular-weight (HMW) adiponectin and to examine interactions with smoking, alcohol drinking, coffee consumption, and menopausal status in a general population.

Design/Setting: Cross-sectional study of 4013 men and 6050 women (40 to 69 years of age).

Main Outcome Measures: The associations of replacing sedentary time with LPA or MVPA on total and HMW adiponectin were analyzed using an isotemporal substitution model.

Results: In men, reallocating 60 minutes of sedentary time to 60 minutes of LPA was associated with 9% and 13% higher total and HMW adiponectin levels even after adjusting for confounders, although such associations were not observed for MVPA. A similar pattern of results was also seen in women. The effect of replacing sedentary time with LPA on adiponectin was clearer in middle/high coffee consumers than in low coffee consumers among women. Although increasing the effect of replacing sedentary time with MVPA on adiponectin was clearer in former/current smokers than in never smokers among men, the replacement effect for MVPA on total adiponectin was clearer in premenopausal women than in postmenopausal women.

Conclusions: Replacing sedentary time with LPA resulted in increased levels of total and HMW adiponectin. The replacement effects for LPA or MVPA were found to be multiply modified by smoking, coffee consumption, and menopausal status.

Abbreviations: BMI, body mass index; HMW, high-molecular-weight; LPA, light-intensity PA; MET, metabolic equivalent; MVPA, moderate- to vigorous-intensity PA; PA, physical activity; Saga J-MICC Study, Saga Japan Multi-Institutional Collaborative Cohort Study.

Adiponectin is a highly abundant adipocytokine in blood and is thought to have beneficial effects of improving insulin resistance and dyslipidemia [1, 2]. Unlike other adipocytokines, circulating adiponectin levels are paradoxically decreased in obesity [3] and other metabolic and cardiovascular diseases [4, 5]. Adiponectin exists in different multimeric forms as either low-molecular-weight, medium-molecular-weight, or high-molecular-weight (HMW) molecules, with HMW adiponectin known to be more biologically active than the smaller forms [6].

Previous findings regarding the effect of physical activity (PA) on adiponectin have been wildly inconsistent [7–9]. Cross-sectional studies have shown that a higher PA is associated with higher total adiponectin levels, even after adjustment for body weight or fat mass [10–13], and some exercise intervention studies have shown that exercise training augmented the total adiponectin levels, despite no reduction in body weight or fat [14–17]. However, there are also several reports showing that the adiponectin concentration was unaffected [18–20] or even decreased [21, 22] by exercise training without concomitant weight loss.

The reasons for these inconsistencies regarding the effects of PA on circulating adiponectin levels remain unclear. One possible reason may be the inclusion of different intensities of exercise training regimens in these previous studies [8]. It has been shown that the adiponectin concentration is regulated by free fatty acids and/or lipolysis [23], and free fatty acids and lipolysis are known to be strongly regulated by the intensity of exercise [24]. Recently, an isotemporal substitution model was developed to perform analyses, as increased time spent in one activity during awaking hours necessarily requires an equal decrease in time spent in another activity [25], making this model extremely useful for investigating the health impact of isotemporal substitution of sedentary behavior time with intensity-specific PA of the same duration [*i.e.*, light-intensity PA (LPA) or moderate- to vigorous-intensity PA (MVPA)] while keeping the total time constant [26, 27]. Therefore, in the current study we sought to examine the replacement effect of sedentary time with either LPA or MVPA on adiponectin levels using this isotemporal substitution model.

Another possible reason for the historically inconsistent results may be heterogeneity of subject characteristics, such as smoking and drinking habits. To our knowledge, there have been no studies investigating the interactions between replacing sedentary time with LPA or MVPA and characteristic factors in a large population. Smoking is known to have an inhibitory effect on adiponectin [10, 28]. However, alcohol drinking [29] and coffee consumption [30, 31] have been associated with high levels of adiponectin. Reduced estradiol concentrations have also been associated with higher adiponectin levels in older adults [32], and postmenopausal women have consistently shown higher adiponectin levels than those of premenopausal women [33]. Based on these reports, we hypothesized that adiponectin-promoting factors (*i.e.*, alcohol drinking, coffee consumption, postmenopausal status) would help clarify the positive association of the replacing effect of LPA or MVPA on adiponectin, whereas adiponectin-inhibiting smoking would moderate this replacement effect.

In the current study, using isotemporal substitution, we investigated the cross-sectional association of replacing sedentary time with either LPA or MVPA on total and HMW adiponectin levels and examined the potential interactions with cigarette smoking, alcohol drinking, coffee consumption, and menopausal status in a large middle-aged population.

1. Materials and Methods

A. Subjects

The current subjects were selected from among 12,068 middle-aged Japanese participants (40 to 69 years of age) of the baseline survey (2005 to 2007) of the Saga Japan Multi-Institutional Collaborative Cohort Study (Saga J-MICC Study). The methods of recruiting subjects in the Saga J-MICC Study have been described in detail elsewhere [34, 35]. In brief, the baseline face-to-face survey was conducted on weekdays or a weekend in a public hall

within the residential areas of the study participants, and the participation rate of the baseline survey of the Saga J-MICC Study was 19.6% (12,068 of 61,447).

Written informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committees at Saga University Faculty of Medicine and the Nagoya University Graduate School of Medicine (a central office of the overall J-MICC Study).

B. Objective Measurement of Habitual PA in Daily Life

On the day of the survey, the subjects were instructed to firmly attach a single-axis accelerometer (Lifecorder; Suzuken, Nagoya, Japan) to a belt or a designated waistband provided for this purpose on the waist just above the midline of the thigh (right or left), during all waking hours for 10 days except when bathing and sleeping. After the accelerometer had been worn for 10 continuous days, the device was retrieved and the recorded PA data were downloaded to a computer and analyzed using the Microsoft Excel software program (Microsoft, Redmond, VA). To eliminate potential reactivity accompanied by wearing the accelerometers, data from the first 3 days in the 10-day wear period were excluded and the data of the latter 7 days were used to analyze the wear times and wear days, with valid accelerometer data defined as ≥ 8 h/d of wear time with ≥ 4 days.

The single-axis accelerometer has been shown to precisely assess PA intensity by detecting 11 incremental levels of acceleration intensities (0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 9) [36]. In the current study, sedentary time was calculated based on an acceleration intensity corresponding to 0.5, because an acceleration intensity of 0.5 is detected by a degree of PA corresponding to <1.8 metabolic equivalents (METs), such as posture changes or light deskwork [36, 37]. The current definition of sedentary behavior is not exactly the same as the general definition of <1.5 METs but is close [38]. The accelerometer can distinctly measure LPA (<3 METs; acceleration intensities, 1–3) and MVPA (>3 METs; acceleration intensities, 4–9) [36, 37]. Accelerometer wear time was calculated as the sum of sedentary time, LPA, and MVPA.

C. Anthropometric Measurements and Self-Administered Questionnaire

The height (to the nearest 0.1 cm) and body weight (to the nearest 0.1 kg) were measured using a portal scale. The body mass index (BMI) was determined by dividing body weight in kilograms by the square of height in meters. The waist circumference at the level of the umbilicus during the light-exhalation phase was measured in a standing position to the nearest 0.1 cm. A self-administered questionnaire that included questions on cigarette smoking, alcohol drinking, coffee consumption, and dietary habits, as well as current medication and disease history, was sent to participants by mail, before the face-to-face survey. The subjects were instructed to bring their completed questionnaires on the day of the survey, and when there were missing or inconsistent answers in the questionnaires a research nurse or nutritionist asked the participants to fill in the blanks or correct the answers. With respect to smoking and alcohol drinking, subjects were first asked about their current status (and cessation time for former smokers or drinkers). Current smokers and drinkers reported their usual cigarette consumption (cigarettes/d) or alcohol drinking (types of alcoholic beverages, amount of beverage consumed per drinking day, and frequency of drinking days), respectively. Total ethanol consumption per day for current drinkers was estimated based on beverage-specific ethanol concentrations, and information on diet was collected using a validated short food frequency questionnaire [39–42]. Coffee consumption was calculated based on the number of cups and frequency of coffee drinking (cups/d). Regarding canned coffee or coffee in plastic bottles, the subjects were instructed to answer by converting 350 and 500 mL to 2 and 3 cups, respectively. The coffee consumption status was categorized as low (<1.0 cup/d), medium (1.0 to 2.9 cups/d), and high coffee consumers (≥ 3.0 cups/d).

D. Blood Sampling and the Adiponectin Assay

Venous blood (21 mL) was drawn from each participant, and within 3 hours of blood sampling, the serum was separated by centrifugation [3000 rpm (1200 × g), 4°C, ≥10 minutes] and stored at −80°C until further use. In the face-to-face survey of the Saga J-MICC Study, the participants were not required to be in a fasting state. Because a previous study has reported that the general inflammatory response (assessed by IL-6 and C-reactive protein) to feeding was minimal, when the blood sample was taken via a single-use needle (instead of using a cannula) [43] and a single-use needle was used for the aforementioned current blood sampling, adiponectin data from nonfasting subjects were included in the current data analyses. The serum concentration of total adiponectin and HMW adiponectin were measured using an ELISA kit (Otsuka Pharmaceutical Company, Tokushima, Japan) [44, 45]. The intra-assay and interassay coefficients of variation for total adiponectin and HMW adiponectin were <15%. All serum samples were measured in duplicate at a single laboratory at the Faculty of Medicine, Saga University.

E. Statistical Analyses

From the 12,068 total participants, we excluded from the current data analysis those with any of the following conditions: total adiponectin not measured (n = 52); HMW adiponectin not measured (n = 7); missing or invalidated PA data (n = 640); a dietary energy intake ≥4000 kcal/d (n = 4); currently using an analgesic antipyretic (n = 480); and those with possible inflammation-related diseases, such as cardiovascular disease (n = 132), stroke (n = 37), diabetes mellitus (n = 572), and cancer (n = 81). Consequently, 10,063 subjects (4013 men and 6050 women) remained for the analysis. Statistical analyses were performed using the SAS software program (version 9.3 for Windows; SAS Institute, Cary, NC). Sex differences in characteristics were examined by t tests (for continuous variables) or χ^2 tests (for categorical variables). For total adiponectin and HMW adiponectin, the natural logarithm value was used in all analyses to minimize the skewness of their distributions, and the resulting geometric mean (and either geometric SD or 95% CI, where appropriate) is presented. The association was separately analyzed by sex. The significance of the univariate correlations of PA indices (LPA and MVPA) or natural log–transformed total and HMW adiponectin levels with the basic characteristics of the subjects was assessed according to the Spearman rank correlation coefficient (ρ).

We first analyzed the cross-sectional multivariate association of each behavior (sedentary time, LPA, or MVPA) with serum adiponectin by multiple linear regression based on a single-factor model with adjustment for wear time [continuous (minutes)], age [continuous (years)], smoking [categorical (never, former, and current smoker)], alcohol drinking [categorical (never/former drinker, current drinker consuming 0.1 to 22.9 or ≥23.0 g of ethanol/d)], coffee consumption [categorical (<1.0, 1.0 to 2.9, and ≥3.0 cups/d)], energy intake [continuous (kcal/d)], and menopausal status [in women: categorical (premenopausal or postmenopausal)] (model 1). Associations were further adjusted for body fat indices of BMI [continuous (kg/m^2)] and waist circumference [continuous (cm)] (model 2).

Second, an isotemporal substitution analysis was performed to investigate the association of substituting either LPA or MVPA for an equal amount of sedentary time on serum adiponectin levels. To investigate the effect of replacing sedentary time with LPA or MVPA, the isotemporal substitution model requires that the wear time, LPA, and MVPA and covariates be simultaneously entered into a multiple linear regression model (only sedentary time is dropped), and the resulting regression coefficient for either LPA or MVPA represents the effect of substituting a given unit of time in LPA or MVPA for an equal amount of time in sedentary behavior. The adjusted percentage changes in adiponectin levels for single-unit increases (60 minutes) in either LPA or MVPA and simultaneous 60-minute decreases in sedentary time were calculated by converting the resulting regression coefficients (β) to [exp (β) − 1] × 100. Similar to the aforementioned analysis using a single-factor model, in the

isotemporal substitution analysis, adjustment was made for wear time (continuous), age (continuous), smoking (categorical), alcohol drinking (categorical), coffee consumption (categorical), energy intake (continuous), and menopausal status (categorical) (in women) (model 3), and additionally BMI (continuous) and waist circumference (continuous) (model 4).

Finally, an interaction analysis was performed to examine whether the effect of replacing sedentary time with either LPA or MVPA is modified by different levels of each subject's characteristic factor, such as cigarette smoking (never, former, and current smoker), alcohol drinking (never/former drinker, current drinker consuming 0.1 to 22.9 and ≥23.0 g of ethanol/d), coffee consumption (<1.0, 1.0 to 2.9, and ≥3.0 cups/d), and menopausal status (premenopausal or postmenopausal). For instance, to examine whether the effect of replacing sedentary time with LPA is modified by smoking, an additional interaction term (LPA × smoking) was included in a multiple regression model with full adjustment including BMI and waist circumference. In these interaction analyses, both intensity-specific PA indices (LPA and MVPA) and three characteristic factors (smoking, alcohol drinking, and coffee consumption) were treated as continuous variables, whereas only menopausal status was treated as a categorical variable. When the interaction analysis results were statistically

Table 1. Characteristics of the Study Subjects

Characteristics[a]	Men (n = 4013)	Women (n = 6050)	P[b]
Age, y	55.8 (8.2)	55.3 (8.2)	0.005
BMI, kg/m²	23.6 (3.0)	22.3 (3.1)	<0.0001
Waist circumference, cm[c]	86.0 (8.0)	80.9 (9.3)	<0.0001
Smoking status, % (n)[d]			
Never	978 (24.4)	5265 (87.0)	<0.0001
Former	1558 (38.8)	297 (4.9)	
Current			
1–19 cigarettes/d	414 (10.3)	319 (5.3)	
20–39 cigarettes/d	911 (22.7)	161 (2.7)	
40+ cigarettes/d	152 (3.8)	7 (0.1)	
Alcohol drinking, % (n)[e]			
Never	655 (16.3)	3380 (55.9)	<0.0001
Former	117 (2.9)	128 (2.1)	
Current			
0.1–22.9 g/d	1467 (36.6)	2260 (37.4)	
23.0–45.9 g/d	896 (22.4)	196 (3.2)	
46.0+ g/d	874 (21.8)	80 (1.3)	
Coffee consumption, % (n)[f]			
<1.0 cup/d	1684 (42.0)	2556 (42.3)	<0.0001
1.0–2.9 cups/d	1312 (32.7)	2266 (37.5)	
≥3.0 cups/d	1017 (25.3)	1227 (20.3)	
Postmenopausal, % (n)[g]	—	4026 (67)	—
Total energy intake, kcal/d	1943 (351)	1517 (228)	<0.0001
Accelerometer data			
Sedentary time, min/d	661 (91)	726 (89)	<0.0001
LPA, min/d	64 (27)	66 (23)	<0.0001
MVPA, min/d	22 (18)	19 (13)	<0.0001
Wear time, min/d	746 (98)	810 (97)	<0.0001
Total adiponectin, μg/mL[h]	7.1 (1.6)	11.9 (1.6)	<0.0001
HMW adiponectin, μg/mL[h]	3.9 (2.1)	8.7 (2.0)	<0.0001

[a]Values are mean (SD) for continuous variables and number (percentage) for categorical variables.
[b]P value for sex differences are based on t tests for continuous variables and χ^2 tests for categorical variables.
[c]Based on 4012 men and 6049 women.
[d]Based on 6049 women.
[e]Based on 4009 men and 6044 women.
[f]Based on 6049 women.
[g]Based on 6042 women.
[h]Geometric mean (geometric SD).

Table 2. Selected Characteristics of Subjects by Quartiles of LPA and MVPA

	Men (n = 4013)							
	LPA (min/d)				MVPA (min/d)			
Characterstics[a]	Q1 (Lowest)	Q4 (Highest)	ρ^b	P^c	Q1 (Lowest)	Q4 (Highest)	ρ^b	P^c
Age, y	56.5	55.5	−0.036	0.024	57.9	55.7	−0.099	<0.0001
BMI, kg/m^2	24.0	23.1	−0.106	<0.0001	23.7	23.4	−0.045	0.005
Waist circumference, cm[d]	87.1	84.4	−0.123	<0.0001	87.3	84.5	−0.125	<0.0001
Current smokers, %	9.7	9.6	−0.006	0.699	11.5	6.8	−0.130	<0.0001
Current drinkers, %[e]	18.8	20.6	0.060	0.000	19.3	21.0	0.028	0.081
Coffee consumers 3+ cups/d, %[f]	6.4	6.6	0.009	0.550	5.8	5.9	0.026	0.095
Postmenopausal, %[g]	—	—	—	—	—	—	—	—
Total energy intake, kcal/d	1862	2028	0.168	<0.0001	1907	1969	0.063	<0.0001
LPA, min/d	36	100	0.968	<0.0001	50	75	0.349	<0.0001
MVPA, min/d	16	29	0.346	<0.0001	6	46	0.968	<0.0001
Total adiponectin, μg/mL[h]	6.6	7.8	0.128	<0.0001	7.0	7.4	0.061	0.0001
HMW adiponectin, μg/mL[h]	3.5	4.5	0.119	<0.0001	3.8	4.1	0.050	0.002

(*Continued*)

significant, then a stratified analysis by the different levels of each characteristic factor was conducted.

A *P* value of <0.05 was considered to be statistically significant.

2. Results

As shown in Table 1, the women tended to be slightly younger than the men and had a lower BMI and waist circumference. The percentage of current smokers was higher among men (36.8%) than women (8.1%), and the percentage of current drinkers was also higher among men (80.8%) than women (41.9%). The coffee consumption status was also different between the sexes. The percentage of postmenopausal women was nearly 70%. The total energy intake was higher in men than in women. The sedentary time, LPA, and wear time were greater in women, whereas MVPA was greater in men. As expected, both the total and HMW adiponectin levels were higher in women than in men. The univariate correlations of basic characteristics with intensity-specific PA indices or with serum adiponectin levels are presented in Tables 2 and 3.

Table 4 shows the results based on a single-factor model with adjustment for wear time, age, cigarette smoking, alcohol drinking, coffee consumption, energy intake, and menopausal status (in women) (model 1), and additionally body fat indices of BMI and waist circumference (model 2). The sedentary time was inversely associated with the total and HMW adiponectin levels, even after adjustment for the BMI and waist circumference, in both sex groups. Whereas positive associations of LPA with total and HMW adiponectin levels remained significant even after adjustment for the two body fat indices (model 2), the associations of MVPA became nonsignificant after that adjustment.

Table 5 shows the results of the isotemporal substitution model indicating the effects of replacing 60 minutes of sedentary time with an equal amount of either LPA or MVPA on total and HMW adiponectin levels. In both men and women, significant and positive associations of substitution effects for LPA were consistently observed, whereas such clear effects were not seen for MVPA. Regarding the replacement effect of LPA, additional adjustment with the BMI and waist circumference decreased the effect size

Table 2.   Selected Characteristics of Subjects by Quartiles of LPA and MVPA (Continued)

Women (n = 6050)							
LPA (min/d)				MVPA (min/d)			
Q1 (Lowest)	Q4 (Highest)	ρ^b	P^c	Q1 (Lowest)	Q4 (Highest)	ρ^b	P^c
56.6	54.3	−0.101	<0.0001	57.7	55.1	−0.118	<0.0001
22.7	22.0	−0.079	<0.0001	22.6	22.2	−0.030	0.019
82.3	79.8	−0.089	<0.0001	82.7	80.0	−0.096	<0.0001
2.8	1.5	−0.073	<0.0001	2.6	1.7	−0.045	0.001
9.8	11.0	0.033	0.010	9.3	10.8	0.043	0.001
4.8	5.4	0.039	0.002	4.2	5.5	0.065	<0.0001
17.7	15.9	−0.056	<0.0001	18.8	16.8	−0.066	<0.0001
1483	1555	0.120	<0.0001	1512	1519	0.013	0.319
39	96	0.968	<0.0001	51	78	0.425	<0.0001
13	25	0.424	<0.0001	6	37	0.968	<0.0001
11.6	12.6	0.057	<0.0001	11.6	12.3	0.042	0.001
8.4	9.6	0.065	<0.0001	8.5	8.9	0.028	0.030

Abbreviation: Q, quartile.

[a]Values are mean (continuous variables) or percentage (categorical variables).

[b]Spearman rank correlation coefficient.

[c]P value for linear trends across quartiles are based on a linear regression analysis for continuous variables and the Mantel test for current drinking, smoking, and menopausal status.

[d]Based on 4012 men and 6049 women.

[e]Based on 4009 men and 6044 women.

[f]Based on 6049 women.

[g]Based on 6042 women.

[h]Geometric mean (geometric SD).

(percentage change) by 4% to 6% in men and 3% to 4% in women, but these associations remained significant after this adjustment. In men, as shown in the results of model 2 for LPA, replacing 60 minutes of sedentary time with an equal duration of LPA was associated with 9% and 13% higher total and HMW adiponectin levels, respectively, even after adjusting for indices of body fat. A similar pattern of substitution effect from switching sedentary time to LPA was also observed in women. Overall, the extent of the substitution effect appeared to be greater for HMW adiponectin levels than total adiponectin levels.

As shown in Table 6, interaction analyses revealed that the effect of substituting sedentary time with LPA on the total adiponectin levels was significantly modified by coffee consumption in women ($P_{\text{interactions}} < 0.05$). Regarding the effect of substituting sedentary time with MVPA, the interaction with cigarette smoking on total and HMW adiponectin levels was statistically significant in men ($P_{\text{interactions}} < 0.05$), whereas a significant interaction with the menopausal status on total adiponectin was detected in women ($P_{\text{interactions}} < 0.05$). Table 7 shows the association of stratified analyses regarding the significant interactions of LPA with coffee consumption in women. Medium (1.0 to 2.9 cups/d) or high (≥3.0 cups/d) coffee consumers showed a greater replacement effect of LPA for increasing adiponectin than low coffee consumers (<1.0 cup/d) (Table 7). Although positive associations with both adiponectin indices were seen for the replacement effect of MVPA among former and current smokers in men, there was a tendency toward an inverse association among never smokers, although the P trend for these associations did not reach statistical significance (Table 8). Additionally, the increasing effect of replacing sedentary time with MVPA on total adiponectin was clearer in premenopausal women than in postmenopausal women.

Table 3. Spearman Rank Correlation Coefficients of the Basic Characteristics of Subjects With Total and HMW Adiponectin, According to Sex

| | Men (n = 4013) | | | | Women (n = 6050) | | | |
| | Total Adiponectin (µg/mL) | | HMW Adiponectin (µg/mL) | | Total Adiponectin (µg/mL) | | HMW Adiponectin (µg/mL) | |
Characteristics	ρ^a	P	ρ^a	P	ρ^a	P	ρ^a	P
Age, y	0.1299	<0.0001	0.1056	<0.0001	0.0966	<0.0001	0.0743	<0.0001
BMI, kg/m^2	−0.3295	<0.0001	−0.2848	<0.0001	−0.2937	<0.0001	−0.2715	<0.0001
Waist circumference, cm	−0.3184	<0.0001	−0.2713	<0.0001	−0.2864	<0.0001	−0.2608	<0.0001
Total energy intake, kcal/d	−0.0001	0.9952	0.0009	0.9544	0.0203	0.1139	0.0163	0.2041
Cigarette smoking[b]	−0.0614	<0.0001	−0.0592	0.0002	−0.0478	0.0002	−0.0467	0.0003
Alcohol drinking[c]	−0.0196	0.2157	−0.0233	0.1411	0.0286	0.026	0.0285	0.0270
Coffee consumption[d]	0.0245	0.1211	0.0265	0.0933	0.0322	0.0123	0.0263	0.0407
Menopausal status[e]	—	—	—	—	0.1038	<0.0001	0.0764	<0.0001

[a]Spearman rank correlation coefficient.
[b]Never, former, and current smokers.
[c]Never or former smokers and current drinker of 0.1–22.9 and 23+ g of ethanol/d.
[d]Low, medium, and high consumer of <1.0, 1.0–2.9, and 3+ cups/d.
[e]Premenopausal or postmenopausal.

3. Discussion

The current study investigated the cross-sectional association of replacing sedentary time with either LPA (<3 METs) or MVPA (≥3 METs) on total and HMW adiponectin levels and further examined potential interactions with cigarette smoking, alcohol drinking, coffee consumption, and menopausal status in a large middle-aged population. One of the major findings of the current study was that replacing 60 minutes of sedentary time with the same period of LPA was linked with 4% to 13% higher total and HMW adiponectin levels, even after additional adjustment with body fat indices in men and women. Furthermore, the substitution effects for either LPA or MVPA were found to be multiply modified by cigarette smoking, coffee consumption, and menopausal status. These results may partially explain

Table 4. The Association of Accelerometer-Determined Sedentary Time and Intensity-Specific PA With Total and HMW Adiponectin Analyzed by a Single Factor Model, According to Sex

| | Men (n = 4013) | | | | | | Women (n = 6050) | | | | | |
| | Total Adiponectin (µg/mL) | | | HMW Adiponectin (µg/mL) | | | Total Adiponectin (µg/mL) | | | HMW Adiponectin (µg/mL) | | |
	% Change[a]	95% CI	P	% Change[a]	95% CI	P	% Change[a]	95% CI	P	% Change[a]	95% CI	P
Sedentary time, h/d												
Model 1	−9	(−11, −7)	<0.0001	−12	(−15, −9)	<0.0001	−6	(−8, −3)	<0.0001	−8	(−11, −4)	<0.0001
Model 2	−6	(−8, −3)	<0.0001	−8	(−11, −4)	<0.0001	−3	(−6, −1)	0.005	−5	(−8, −1)	0.006
LPA, h/d												
Model 1	14	(10, 18)	<0.0001	20	(14, 27)	<0.0001	8	(4, 12)	<0.0001	14	(8, 20)	<0.0001
Model 2	9	(5, 13)	<0.0001	13	(8, 19)	<0.0001	5	(1, 8)	0.008	9	(4, 15)	0.0004
MVPA, h/d												
Model 1	9	(4, 15)	0.0008	11	(3, 20)	0.006	9	(3, 15)	0.003	6	(−2, 15)	0.127
Model 2	4	(−1, 9)	0.085	6	(−2, 14)	0.146	5	(0, 10)	0.072	2	(−6, 10)	0.667

Model 1 (single factor model) was adjusted for wear time, age, smoking, alcohol drinking, coffee consumption, total energy intake, and menopausal status (in women). Model 2 (single factor model) was adjusted for all covariates included in model 1 plus BMI and waist circumference.
[a]The percentage change was calculated by converting the regression coefficient (β) to [exp(β) − 1] × 100.

Table 5. The Association of Substituting 60 Min of Sedentary Time With the Same Amount of Time in LPA or MVPA With Total and HMW Adiponectin Levels Using Isotemporal Substitution

	Model 3						Model 4					
	Sedentary to LPA			Sedentary to MVPA			Sedentary to LPA			Sedentary to MVPA		
Outcome (Adiponectin)	% Change[a]	95% CI	P	% Change[a]	95% CI	P	% Change[a]	95% CI	P	% Change[a]	95% CI	P
Men												
Total adiponectin	13	(9, 17)	<0.0001[b]	4	(−1, 10)	0.125	9	(5, 13)	<0.0001[b]	1	(−4, 6)	0.623
HMW adiponectin	19	(13, 26)	<0.0001[b]	−4	(−4, 13)	0.301	13	(7, 19)	<0.0001[b]	1	(−6, 9)	0.783
Women												
Total adiponectin	7	(3, 11)	0.0006[b]	5	(−1, 11)	0.108	4	(0, 8)	0.03[b]	3	(−3, 9)	0.350
HMW adiponectin	14	(8, 21)	<0.0001[b]	−0.9	(−9, 8)	0.831	10	(4, 16)	0.0003[b]	−3	(−11, 5)	0.393

Model 3 was adjusted for wear time, age, cigarette smoking, alcohol drinking, coffee consumption, total energy intake, and menopausal status (in women). Model 4 was adjusted for all covariates included in model 3 plus BMI and waist circumference.

[a]Percentage change (95% CI) in adiponectin levels for a 60-min increase in the substituted LPA or MVPA for an equal amount (60 min) of sedentary time (see Materials and Methods).

[b]$P < 0.05$.

the inconsistency of previous reports on the association of PA with adiponectin that usually investigated the effect of a certain intensity PA (*e.g.*, MVPA) in a small sample size of a certain type of subjects.

The increase in adiponectin levels by replacing sedentary time with LPA may be attributed to increased adiponectin secretion from adipose tissue. As mentioned in the introduction section, the pharmacological suppression of lipolysis (induced by the drug acipimox) reduced circulating adiponectin levels, indicating that lipolytic activity is important in adiponectin synthesis and secretion [23] and LPA is known to be able to induce greater peripheral lipolytic activity than MVPA [24]. Consistently, a rodent study compared the effects of low-intensity (treadmill speed 25 m/min) and high-intensity (30 m/min) exercise training for 12 weeks and showed that low-intensity exercise had an equivalent (when rats exercised 2 d/wk) or even greater (when rats exercised 5 d/wk) effect on the extent of increase in adiponectin mRNA expression in adipose tissue [46]. Thus, LPA might increase adiponectin levels, probably through an increased expression of the adiponectin gene, presumably due to the enhancement of lipolysis by habitual LPA.

Table 6. *P* Interaction Between Replacing Sedentary Time With Either LPA or MVPA and Four Characteristic Factors on Total and HMW Adiponectin

	Men (n = 4008)		Women (n = 6034)	
	Total Adiponectin $P_{\text{interaction}}$	HMW Adiponectin $P_{\text{interaction}}$	Total Adiponectin $P_{\text{interaction}}$	HMW Adiponectin $P_{\text{interaction}}$
Cigarette smoking				
Sedentary to LPA	0.327	0.345	0.496	0.947
Sedentary to MVPA	0.011[a]	0.003[a]	0.981	0.942
Alcohol drinking				
Sedentary to LPA	0.327	0.241	0.634	0.588
Sedentary to MVPA	0.325	0.251	0.690	0.865
Coffee consumption				
Sedentary to LPA	0.397	0.341	0.017[a]	0.108
Sedentary to MVPA	0.306	0.251	0.339	0.758
Menopausal status				
Sedentary to LPA	—	—	0.488	0.677
Sedentary to MVPA	—	—	0.011[a]	0.094

[a]$P_{\text{interaction}} < 0.05$.

Table 7. The Association of Substituting 60 Min of Sedentary Time With the Same Amount of Time in LPA With Total and HMW Adiponectin Levels, Stratified by Coffee Consumption in Women

	n	% Change[a]	95% CI	P	P_interaction	% Change[a]	95% CI	P	P_interaction
		Total Adiponectin				**HMW Adiponectin**			
Coffee consumption, cups/d									
<1.0	2553	1	(−4, 7)	0.709		7	(−1.3, 16)	0.100	
1.0–2.9	2258	6	(−0.3, 12)	0.061	0.017	13	(4, 24)	0.005	0.1080
≥3.0	1223	8	(−0.5, 17)	0.065		12	(−0.4, 26)	0.059	

[a]Percentage change (95% CI) in adiponectin levels for a 60-min increase in the substituted LPA for an equal amount (60 min) of sedentary time.

One of the major findings of the current study is that coffee consumption is an effect modifier of replacing sedentary time with LPA on adiponectin in women. Coffee consumption has been associated positively with adiponectin [30, 31]. The current result showed that the positive association of replacing sedentary time with LPA on the total and HMW adiponectin levels was clearer in medium (1.0 to 2.9 cups/d) or high (≥3.0 cups/d) coffee consumers than in low coffee consumers (<1.0 cup/d) in women. A possible mechanism underlying this interaction has been suggested, although the precise mechanisms remain to be clarified. As discussed above, lipolysis in adipose tissue, which can be strongly induced by LPA, plays an important role in adiponectin synthesis and secretion. Similar to LPA, coffee is known as a lipolysis inducer [47, 48]. Caffeine or other constituents of coffee, such as chlorogenic acid, may therefore be involved in the increased lipolysis after coffee intake [47]. In the current study, the positive correlations of coffee consumption with total and HMW adiponectin appeared to be stronger in women than those in men (see Table 3), and these sexually distinct effects of coffee consumption on serum adiponectin may be a reason for the sex-specific finding. Therefore, the combination of two lipolytic factors (LPA and coffee consumption) might induce even greater lipolysis, and the augmented lipolysis induced by these two factors might promote adiponectin secretion from adipose tissue in women.

In the current study, interaction analyses showed that the positive association of replacing sedentary time with MVPA on adiponectin indices was clearer in former or current smokers

Table 8. The Association of Substituting 60 Min of Sedentary Time With the Same Amount of Time in MVPA With Total and HMW Adiponectin Levels, Stratified by Cigarette Smoking (in Men) or Menopausal Status (in Women)

	n	% Change[a]	95% CI	P	P_interaction	% Change[a]	95% CI	P	P_interaction
		Total adiponectin				**HMW Adiponectin**			
Men									
Cigarette smoking									
Never	978	−6	(−13, 2)	0.166	0.011	−10	(−21, 2)	0.098	0.003
Former	1556	5	(−2, 14)	0.180		8	(−4, 21)	0.213	
Current	1474	5	(−5, 17)	0.317		10	(−7, 29)	0.255	
Women									
Menopausal status									
Premenopausal	2014	17	(5, 31)	0.003	0.011	11	(−5, 29)	0.203	0.094
Postmenopausal	4020	−2	(−8, 5)	0.638		−7	(−16, 2)	0.126	

[a]Percentage change (95% CI) in adiponectin levels for a 60-min increase in the substituted MVPA for an equal amount (60 min) of sedentary time.

than in never smokers among men. Cigarette smoking has been reported to have a suppressive effect on the circulating adiponectin levels in men [28]. We therefore hypothesized that cigarette smoking would attenuate the positive association of replacing sedentary time with PA indices on adiponectin. However, our results rejected that hypothesis. As a possible explanation for the unexpected results, smoking and nicotine are known to promote lipolysis in adipocytes and promote the release of free fatty acids [49], and lipolysis can promote adiponectin secretion. Therefore, smoking-induced lipolysis might aid in increasing the adiponectin response to habitual PA in current smokers. We are unable to explain the possible mechanisms in former smokers. However, the current results suggest that a beneficial effect of replacing sedentary time with MVPA on adiponectin can be expected even in former or current smokers among men.

Interestingly, replacing sedentary time with MVPA tended to be associated with lower (not higher) adiponectin levels in male never smokers, although this association was not statistically significant. This result is in line with the findings of previous exercise intervention studies showing that moderate training decreased the adiponectin concentration in healthy (nonsmoker) men [22]. In that previous study, the whole-body insulin sensitivity was improved after exercise, despite a decreased level of adiponectin [22]. Another report also showed that exercise intervention slightly decreased the serum adiponectin levels (albeit nonsignificantly); however, the mRNA expression of adiponectin receptors was upregulated in skeletal muscle [50]. Given these previous and present results, a physiological adaptation to MVPA might occur mainly in muscle (adiponectin receptors) rather than in adipose tissue in never smoker men, and it is theoretically possible that the increased binding of adiponectin to the muscle adiponectin receptors and the concomitant degradation of adiponectin after the receptor binding might act to decrease circulating adiponectin.

Unlike the effect of replacing sedentary time with MVPA on adiponectin in the male never smokers, replacing sedentary time with LPA was insignificantly but positively (not inversely) associated with total and HMW adiponectin in the never smoker subjects (data not shown), and that is considered to be a reason for the nonsignificant interaction between LPA and smoking status. LPA might not provide sufficient physiological stimulation to induce the muscle adaptation (*i.e.*, an increase in adiponectin receptors) in the male never smokers. Further studies are needed to elucidate the regulatory mechanisms balancing MVPA-induced improvement in muscle insulin sensitivity and circulating adiponectin concentrations.

The current study revealed that menopausal status can modulate the replacement effect of sedentary time with MVPA on adiponectin in women. We hypothesized that a clearer positive association of replacing sedentary time with PA on adiponectin would be observed in postmenopausal women than in premenopausal women, as postmenopausal women are assumed to have lower estradiol levels. However, in contrast to this hypothesis, the replacing effect for MVPA on adiponectin was blunted (not enhanced) in postmenopausal women compared with premenopausal women. The current univariate analysis showed that the adiponectin concentration levels were significantly higher in postmenopausal women than in premenopausal women (total adiponectin, $\rho = 0.10$, $P < 0.0001$; HMW adiponectin, $\rho = 0.08$, $P < 0.0001$; Table 3). This result is consistent with the findings of a previous report showing that postmenopausal women had higher adiponectin levels than did premenopausal women [33]. We speculate that postmenopausal women had higher adiponectin concentrations than premenopausal women and might therefore have had little room left for increasing their adiponectin concentration by MVPA. Additionally, moderate-intensity exercise for 12 weeks did not affect the serum adiponectin levels in postmenopausal women [20], consistent with the current results.

The major strengths of the current study are the large sample size, objectively measured intensity-specific PA, measurements of two types of adiponectin (total and HMW), and usage of an isotemporal substitution model. There are also several limitations to the current study that warrant mention. This study was a cross-sectional study, and we were unable to make inferences regarding causality. The present subjects were not required to be in a fasting state, and their attendance at the face-to-face survey (in which blood sampling was conducted) was not arranged at a specific time of day. Thus, the blood adiponectin levels may have been

influenced by the fasting status and/or diurnal variation. Of note, these potential variations can attenuate the associations of PA and adiponectin levels. Additionally, adjustment was made for BMI and waist circumference, which are clearly correlated with body fat but not strict markers of the body fat content. Finally, we examined neither the gene expression of adiponectin in adipose tissue nor its receptors in skeletal muscle or liver, which may be involved in the control of circulating adiponectin levels.

In conclusion, the current results suggest that replacing 60 minutes of sedentary time with the same duration of LPA was associated with 9% and 4% higher total adiponectin levels, and 13% and 10% higher HMW adiponectin levels in men and women, respectively, even after adjusting for BMI and waist circumference. The interaction analyses suggested that the replacement effect of sedentary time with LPA was modified by coffee consumption in women, whereas the replacement effect of sedentary time with MVPA was modified by cigarette smoking in men and menopausal status in women. These results partially explain the inconsistency in previous reports regarding the association of PA with adiponectin. Further longitudinal studies in a large general population are warranted to confirm the associations suggested by the current study.

Acknowledgments

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