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Original Article

Combined effects of obesity and objectively-measured daily physical activity on the risk of hypertension in middle-aged Japanese men: A 4-year prospective cohort study

Takuji Adachi [a], Kuniyasu Kamiya [a], Daichi Takagi [a], Hironobu Ashikawa [a], Masaya Hori [a], Takaaki Kondo [b], Sumio Yamada [c,*]

[a] Program in Physical and Occupational Therapy, Nagoya University Graduate School of Medicine, 1-1-20, Daiko-minami, Higashi-ku, Nagoya 461-8673, Japan
[b] Department of Pathophysiological Laboratory Sciences, Nagoya University Graduate School of Medicine, 1-1-20, Daiko-minami, Higashi-ku, Nagoya 461-8673, Japan
[c] Department of Health Sciences, Nagoya University Graduate School of Medicine, 1-1-20, Daiko-minami, Higashi-ku, Nagoya 461-8673, Japan

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ABSTRACT

Background: The combined effects of physical inactivity and obesity on hypertension have been recognized; however, previous studies evaluated physical activity using questionnaires. We aimed to examine the effects of physical activity, measured using an accelerometer, and obesity on hypertension onset.
Methods: At baseline, 426 middle-aged Japanese men who were not on antihypertensive medications were included. Physical activity was measured for 7 consecutive days using an accelerometer. Mean daily moderate to vigorous physical activity (MVPA) and step count (SC) were calculated. Low MVPA and low SC were each defined as the first tertile. Obesity was defined as ≥25 kg/m2 of body mass index. The onset of hypertension was defined as receiving antihypertensive agents during the 4-year follow-up. The combined effects of obesity and physical inactivity on hypertension were examined using Cox regression analysis. Potential confounders included age, smoking, alcohol consumption, daily salt intake, dyslipidemia, diabetes mellitus, and systolic and diastolic blood pressures.
Results: Cox regression analysis revealed that both obesity and low MVPA predicted hypertension in patients, independent of confounders (hazard ratio [HR]: 2.64, 95% confidence interval [CI]: 1.08–6.42, p = 0.033), unlike obesity alone (HR: 1.50, 95% CI: 0.50–3.26, p = 0.590). Stratification by obesity and SC revealed similar hypertension risks among the two groups (Obesity with low SC [HR: 2.10, 95% CI 0.88–5.24, p = 0.089]; Obesity without low SC [HR: 1.72, 95% CI 0.93–4.01, p = 0.082]).
Conclusions: Here, findings suggest that the coexistence of obesity and decreased MVPA may increase the risk of hypertension onset.

Introduction

Hypertension is one of the leading risk factors of cardiovascular diseases, including heart disease and stroke [1]. In East Asian countries, the prevention of hypertension is a particularly important issue because there is a higher incidence of stroke in these countries than in Western countries. Since the 1960s, blood pressure levels in the Japanese population have gradually decreased along with a reduction in stroke mortality [2]. However, a nation-wide study that was recently conducted in Japan found that the decrease in blood pressure levels among Japanese men aged ≥50 years has been modest compared to that in both women and younger individuals [3]. Specifically, the prevalence of hypertension among men in their 50s increased from 54.9% in 2000 to 63.2% in 2010 [3]. These data suggest that hypertension remains an important public health concern in Japan.

Lifestyle modification is the basis for preventing many chronic health conditions such as hypertension. Overweight or obesity and physical inactivity are acknowledged as lifestyle factors that induce high blood pressure [4,5]. The process involves a hypertrophic adipose tissue, which releases inflammatory cytokines and reduces secretion of adiponectin, thus, promoting mechanisms to increase

* Corresponding author at: Department of Health Sciences, Nagoya University Graduate School of Medicine, 1-1-20, Daiko-minami, Higashi-ku, Nagoya 461-8673, Japan.
E-mail address: yamadas@met.nagoya-u.ac.jp (S. Yamada).

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blood pressure, such as insulin resistance or endothelial dysfunction [6]. By contrast, physical activity has an inverse relationship with each of these mechanisms [7–10]; therefore, the combination of obesity and physical inactivity may result in an increased risk of hypertension. In a previous cross-sectional study conducted in China, higher body mass index (BMI) and lower level of physical activity were found to be independently associated with hypertension, after adjusting for socioeconomic factors and diabetes mellitus [11]. Another cohort study that was conducted in Finland found an increased risk of hypertension among subjects with higher BMI and lower physical activity [12]. However, physical activity in these studies was determined through the use of a questionnaire. Determination of the possible combined effects of high BMI and low level of physical activity using a more objective means of measurement, has not been previously investigated.

Given the mechanisms that likely determine the effects of physical activity on vascular health, the promotion of daily physical activity at an optimal level of intensity is likely a key factor in the prevention of hypertension. Moderate to vigorous physical activity (MVPA), generally defined as activity with an intensity of >3 metabolic equivalents (such as brisk walking or aerobics) [13], has significant favorable effects on blood pressure. Studies have demonstrated an inverse relationship between MVPA, rather than total energy expenditure or sedentary time [7,8], and insulin resistance, which is associated with hypertension [14]. Additionally, it has been reported that increased blood flow resulting from moderate-intensity physical activity augments endothelium-dependent vasodilation through increased production of nitric oxide [10]. Since there is a threshold of blood flow and pressure at which vasodilation is induced [15], MVPA plays an important role in nitric oxide production. These findings suggest that a low level of MVPA is an important risk factor of hypertension.

In light of the above evidence, we hypothesized that the combination of obesity and low daily MVPA in individuals would be associated with the future onset of hypertension. The goal of this study was to examine the combined effects of obesity and accelerometer-measured physical activity on the onset of hypertension in a cohort of middle-aged Japanese men.

Subjects, materials, and methods

Study population

Participants were men who met the inclusion criteria including being employees of the same company, aged 30–59 years, who were not currently on antihypertensive medication. Volunteers were recruited using inter-office e-mail and bulletins, and all participants provided written informed consent.

Measurement of daily physical activity

The baseline physical activity of each participant was measured for 7 consecutive days using an electrical accelerometer (Kenz Lifecorder, Suzuken, Nagoya, Japan). Good reliability and validity of this device have been reported [16,17]. All measurements were performed in autumn to avoid seasonal variations. The mean daily duration of MVPA and step count for each participant were calculated. The intensity of physical activity was categorized into eleven levels (0, 0.5, 1–9) based on the acceleration pattern. An acceleration intensity of >4 is considered to represent MVPA (activity at an intensity of >3 metabolic equivalents) [18]. Participants were asked to wear the accelerometer for 24 h/day for 1 week, except when they were bathing and sleeping, and to continue their usual daily activities during this time. Participants were blinded to their daily step count and level of MVPA during the 7-day measurement period in order to avoid biasing their PA.

Annual health examination

Most companies in Japan require employees to undergo an annual health examination. Baseline data on BMI, blood pressure, history of cigarette smoking, and frequency of alcohol consumption was obtained from the annual health examination of the participants which was performed during spring of the same year that the physical activity measurement for the present study was taken.

Body weight and height were also collected and were obtained with the participant wearing light indoor clothing but no shoes. BMI was subsequently calculated as body weight in kilograms divided by height in meters squared. Obesity was defined as BMI $\geq$ 25 kg/m2.

Each participant was required to remain seated during blood pressure measurement, which was performed using an electrical sphygmomanometer in accordance with the Japanese Society of Hypertension Guidelines [19]. History of cigarette smoking and frequency of alcohol consumption were assessed using a questionnaire. Lipid profile, blood glucose levels, and hemoglobin A1c levels were determined from each blood sample.

Daily salt intake

Daily salt intake was measured along with PA at baseline. Daily salt intake was measured via the ion-selective electrode method using a self-monitoring device (GENEN Monitor, Kono ME Institute, Kawasaki, Japan). The reliability and validity of this device has been reported previously [20], and this method is one of the three evaluation methods of salt intake that is recommended by the Japanese Society of Hypertension Guidelines [21]. The participants were instructed to void completely and discard the urine before going to bed, and to collect overnight urine of approximately 8 h in a 1-l urine cup. After waking, the participants voided and placed the urine in the urine cup, adding any urine they had voided overnight. The patients were asked to collect their urine for approximately 8 h and to set the salt monitoring device. The estimated salt levels were recorded for 3 consecutive days, and the mean daily salt intake (total salt intake over three days/3) was calculated for each participant.

Outcome

The main study outcome was the onset of hypertension, which was defined as diagnosis made by a physician and receiving antihypertensive medication at any time during the 4-year period after baseline assessment. In Japan, medical receipts are collected monthly by health insurance unions. These receipts describe any medical treatment that is administered to a patient and its corresponding fee. In this study, information on the prescription of antihypertensive, lipid-lowering, or antidiabetic drugs was collected based on information found in the receipts.

Medications were coded according to the Anatomical Therapeutic Chemical Classification System (ATC). ATC codes C02, C03, C07, C08, and C09 were selected as antihypertensive medications. Because indications for being prescribed these medications might include conditions other than hypertension, participants who were recorded as having hypertension were also diagnosed by a physician.

Statistical analysis

Participants with missing data were excluded. The Shapiro–Wilk test was used to determine data distribution. Continuous variables, with or without normal distribution, were described as either the mean $\pm$ standard deviation or median [inter-quartile ranges (IQR)]. Characteristics of the study partici-

Table 1
Characteristics of the study participants.

	Overall (N = 426)	Non obesity (n = 350)	Obesity (n = 76)	p
Age, years	49 [46–53]	51 [46–54]	47 [43–51]	<0.001
BMI, kg/m^2	22.4 [21.0–24.4]	21.8 [20.7–23.3]	26.4 [25.6–27.6]	<0.001
Obesity, %	17.8	0	100	<0.001
Smoking, %	14.3	14.3	14.3	0.993
Drinking (everyday), %	28.7	29.8	25.0	0.282
Salt intake, g/d	10.5 [9.1–12.0]	10.3 [8.9–11.7]	11.6 [10.6–12.7]	<0.001
Systolic BP, mmHg	118 [110–126]	116 [109–124]	125 [118–128]	<0.001
Diastolic BP, mmHg	73 [66–80]	72 [65–80]	76 [73–84]	<0.001
Triglyceride, mg/dL	82 [59–118]	79 [58–109]	82 [59–118]	<0.001
HDL cholesterol, mg/dL	59 [49–68]	60 [51–71]	51 [47–56]	<0.001
LDL cholesterol, mg/dL	121 [103–140]	119 [103–139]	130 [116–141]	0.012
Blood glucose, mg/dL	92 [86–97]	92 [86–96]	92 [86–97]	0.626
HbA1c, %	5.4 [5.2–5.6]	5.4 [5.2–5.6]	5.5 [5.3–5.7]	0.111
Dyslipidemia, %	7.3	7.3	7.3	0.951
Diabetes mellitus, %	1.8	1.4	3.8	0.148
MVPA, min/d	31.8 [22.2–45.6]	33.4 [22.8–38.4]	27.1 [20.4–38.4]	0.006
SC, steps/d	8463 [6926–10756]	8652 [6988–10878]	8497 [6943–10664]	0.048

BMI, body mass index; BP, blood pressure; HDL high-density lipoprotein; LDL, low-density lipoprotein; Hb, hemoglobin; MVPA, moderate to vigorous physical activity; SC, step count.

pants with respect to obesity were compared using the Student's t-test, Mann–Whitney U-test, or chi-square test.

The cumulative incidence rate was analyzed to account for obesity and low MVPA or low step count using the Kaplan–Meier method, followed by the log-rank test. The combined effect of obesity and physical inactivity was analyzed using multivariate Cox regression analysis. Low MVPA and low step count in this study were defined as the lowest tertiles of the daily duration of MVPA and step count, respectively. Cox regression analysis was performed with the study outcome as a dependent variable, and the combination of obesity and low MVPA or low step count, age, cigarette smoking, daily alcohol consumption, daily salt intake, dyslipidemia, diabetes mellitus, systolic blood pressure and diastolic blood pressure, at baseline, as independent variables.

All statistical analyses were carried out with Stata 15 (Stata Corporation, Texas, USA). A p value of <0.05 was considered statistically significant.

Results

Of 436 male volunteers who participated in the baseline survey, 426 were included in the analysis, after exclusion of individuals with missing data (Fig. 1). Characteristics of the study participants are presented in Table 1. The mean age was 49 years and the prevalence of obesity was 17.8%. The median MVPA was 31.8 [IQR: 22.2–45.6] min/d, and <24.6 min d defined low MVPA. Median step count was 8463 [IQR: 6926–10756] steps/d, and <7377 step/d defined low step count.

During the 4-year follow-up period, 43 participants (10.1%) started ingesting an antihypertensive agent. None of the participants experienced a stroke or cardiac disease during the follow-up. Fig. 2 shows Kaplan–Meier estimates of cumulative events according to obesity and physical inactivity. There was a significant difference in the cumulative event rate among the four groups that had been stratified by obesity and low MVPA (p = 0.012) and by obesity and low step count (p = 0.028).

Results of the Cox proportional hazard model to examine the relationship between onset of hypertension and the combination of obesity and physical inactivity are presented in Fig. 3. Combined obesity and low MVPA was an independent predictor of the onset of hypertension, even after adjusting for potential confounders (HR 2.64, 95% CI 1.08–6.42, p = 0.033), while obesity without low MVPA was not (HR 1.50, 95% CI 0.50–3.26, p = 0.590) (Fig. 3A). By contrast, when stratified by obesity and step count, participants with obesity had similar risks of hypertension, regardless of the low step count (obesity with low step count [HR 2.10, 95% CI 0.88–5.24, p = 0.089]; obesity without low step count [HR 1.72, 95% CI 0.93–4.01; p = 0.082]) (Fig. 3B).

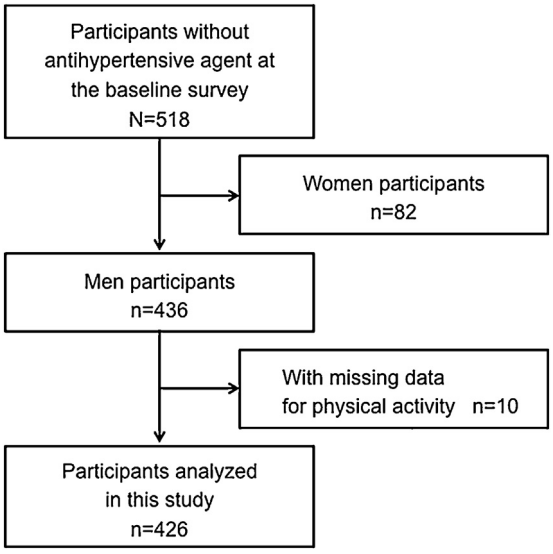

Fig. 1. Flow diagram of the study participants.

Discussion

The major finding of this study was that the combination of obesity and an objectively-measured low MVPA predicted the incidence of hypertension, independent of potential confounders. Despite the relatively small sample size, this study provides evidence to support the idea that weight reduction, integrated with the promotion of MVPA, might be an effective strategy to prevent hypertension in obese individuals.

Results of the present study are in line with previous reports that identified the combined effects of a higher BMI and lower physical activity on hypertension [11,12]. In these previous studies, however, physical activity was evaluated using a questionnaire, and the relationship between the risk of hypertension and the specific combination of obesity and low MVPA was not investigated. Therefore, in our study, physical activity was objectively measured using an electrical accelerometer to stratify the participants. As a result, the combination of obesity and low level of objectively measured MVPA

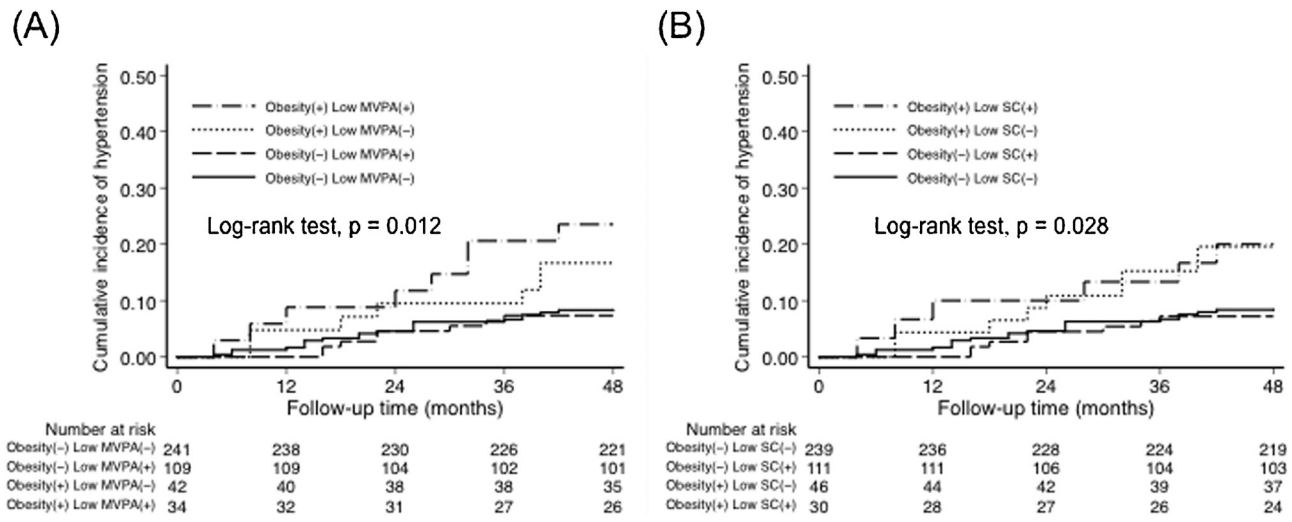

Fig. 2. Kaplan–Meier estimates of cumulative events rate during four years follow-up.
Low MVPA and low SC were defined as daily MVPA < 24.6 min d and SC < 7377 steps/d, respectively.
MVPA, moderate to vigorous physical activity; SC, step count.

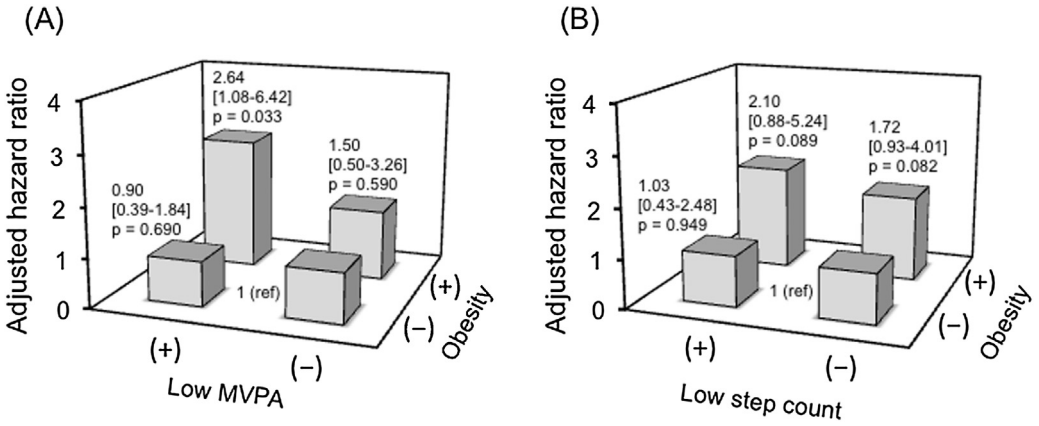

Fig. 3. Hazard ratios of hypertension onset according to obesity and physical activity level.
Hazard ratios are adjusted for age, smoking, drinking, daily salt intake, dyslipidemia, diabetes mellitus, systolic blood pressure and diastolic blood pressure at baseline. 95% confidence interval is presented in brackets.
MVPA, moderate to vigorous physical activity.

was associated with an increased risk of hypertension over a 4-year follow-up, but neither obesity nor low MVPA alone were associated with an increased risk of developing hypertension. These results suggest the importance of decreased MVPA in obese individuals as a contributor to hypertension onset.

The relationship between changes in BMI and physical activity level and hypertension onset is a remaining concern that was not investigated in the present study. A recent meta-analysis has suggested the association of weight gain with the risk of hypertension [22]. Additionally, another cohort study demonstrated the effects of change in physical fitness on the risk of developing hypertension [23]. However, because physical activity for each subject was assessed only once at baseline, the association between the change in exposure and outcomes could not be examined in this study. Moreover, a 4-year follow-up appears inadequate in addressing this concern. Further cohort studies with longer follow-ups and repeated assessments of both BMI and physical activity will clarify the risk of hypertension based on the change of BMI and physical activity level over time.

The release of inflammatory cytokines, and reduced adiponectin secretion from hypertrophic adipose tissue have been considered as major fundamental pathways of hypertension in obese individuals [6]. These mechanisms increase the blood pressure via increased insulin resistance, activation of SNS and RAAS, and endothelial dysfunction [6]. Therefore, the suppression of these pathways by shrinking the size of the hypertrophic adipose tissue is a key mechanism in preventing hypertension. Physical activity is a core element of weight reduction [24], and also has an inverse relationship with SNS and RAAS activity [9]. Additionally, physical activity improves endothelial function by increasing shear stress on the vascular endothelial cells. MVPA may be essential for nitric oxide production because there is a threshold of blood flow and pressure for inducing vasodilatory response [15]. Indeed, moderate-intensity physical activity induces endothelium-dependent vasodilation through increased production of nitric oxide [10]. These favorable effects of MVPA on reduced vascular resistance may explain the results of the multivariate analysis in which obesity without decreased MVPA was not associated with the onset of hypertension. In contrast, step count did not affect the risk of hypertension in the present study. A recent meta-analysis demonstrated that the relationship of sedentary time with the risk of cardiovascular disease is nonlinear with an increased risk only at very high levels (sedentary time >10 h/d) [25]. Therefore, the association between step count and risk of hypertension may be

attenuated possibly because of the inclusion of relatively physically active volunteers in this study.

Salt sensitivity, defined as an increase in blood pressure in response to increased salt intake, is a possible factor that may have influenced our results. Central obesity is associated with increased salt sensitivity [26], and its causal effects have been reported [27]. In addition, a previous study found that individuals who were physically inactive showed a greater blood pressure response to salt consumption [28]. Excessive weight and physical inactivity are both major risk factors in insulin resistance [8,29] and the activation of SNS and RAAS [9,30], which results in enhanced salt sensitivity [31,32]. In general, Asians have a higher salt intake than Westerners [33]. Moreover, the high prevalence of increased salt sensitivity due to genetic characteristics has been recognized in Asian populations [34]. Therefore, reduction of salt intake through lifestyle modifications, including weight loss and promotion of physical activity, seems extremely important in preventing hypertension in overweight Asian people.

There are several limitations to this study that should be mentioned. First, because the subjects voluntarily participated in the cohort study, there is a possibility that people who were interested in health were more likely to be included compared to the general population. Indeed, the baseline prevalence of obesity in this study (17.8%) seems to be lower than that in Japanese men of the same age group. This selection bias could limit the generalizability of the results of this study. Additionally, further studies need to be performed in other age groups and/or female individuals because the study participants were men aged approximately 50 years. Second, the operational definition of hypertension could lead to an overestimation or underestimation of the relationship between exposure and outcomes. Although similar definitions of hypertension have also been used in previous reports [35,36], there is a possibility of misclassifying a hypertensive patient, who has high blood pressure but does not take antihypertensive medication, as a non-hypertensive patient. The inclusion of patients with baseline systolic or diastolic blood pressure $\geq$ 140 or 90 mmHg may be another problem related to this definition. Third, the relatively small sample size can cause errors of inference and inadequate power for analysis. Fourth, there may be confounders that were not measured in this study. For instance, we did not assess nutritional factors and socio-demographic variables such as educational achievement or economic status. Finally, the causal relationship between the combination of weight reduction and promotion of MVPA and the reduced risk of hypertension will need to be established through intervention studies.

In conclusion, we found that the combination of patient obesity and low daily MVPA, evaluated using an accelerometer, predicted the onset of hypertension, but obesity without low MVPA did not. Findings from this study suggest that the coexistence of obesity and decreased MVPA may increase the risk of hypertension onset.

Author contributions

Takuji Adachi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing.

Kuniyasu Kamiya: Data curation, Formal analysis, Investigation, Validation, Visualization, Writing - review & editing.

Daichi Takagi: Data curation, Investigation, Writing - review & editing

Hironobu Ashikawa: Data curation, Investigation, Writing - review & editing.

Masaya Hori: Data curation, Formal analysis, Writing - review & editing

Takaaki Kondo: Conceptualization, Methodology, Project administration, Writing - review & editing.

Sumio Yamada: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing - review & editing.

Ethical statement

The study protocol was approved by the Ethics Committee of the School of Health Sciences, Nagoya University (approval number: 14–508). All study participants provided written informed consent. We have read and have abided by the statement of ethical standards for manuscripts submitted to the Obesity Research & Clinical Practice.

Declaration of interest

None.

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