the extent of leisure time activity exerted a positive influence on VO_2. Therefore, it seems reasonable to suggest that mortality among a proportion of the Japanese population may possibly be decreased simply by improving oxygen uptake at VT through the promotion of exercise habits.

A relationship between maximal oxygen uptake and body composition has been reported in the literature. Significant relationships between maximal oxygen uptake and body fat percentage were noted in Japanese junior high school boys and girls [23], African-American adolescents [24] and Danish women [25]. In an earlier study, we also found that maximal oxygen uptake was significantly correlated with body fat percentage as measured by dual X-ray absorptiometry [17]. Although we could not infer causality between oxygen uptake at VT and body fat percentage and we could not directly measure visceral fat area by computed tomography in this study, an excess of body fat, which is expressed as body fat percentage (%), may be an excess weight and play a critical role in determining oxygen uptake at VT. This result suggests that body fat percentage may be a good predictor for estimating oxygen uptake at VT in Japanese.

In conclusion, the mean values reported here may provide a useful database for evaluating VT in Japanese adult subjects. Although oxygen uptake and work rate at VT in subjects with exercise habits were significantly higher than those in subjects without exercise habits after age had been adjusted for, there were no significant differences in oxygen uptake at VT in men in their 50s and in women >50 years. In addition, this study was a cross-sectional—not a longitudinal—study. Further prospective investigation studies to evaluate the relationship between VT and exercise habits should be carried out in the general Japanese population.

Acknowledgments This research was supported in part by Research Grants from the Ministry of Health, Labor, and Welfare, Japan.

References

1. Miyatake N, Takahashi K, Wada J, Nishikawa H, Morishita A, Suzuki H, et al. Daily exercise lowers blood pressure and reduces visceral fat in overweight Japanese men. Diabetes Res Clin Pract. 2003;62:149–57.
2. Barnard RJ, Ugianskis EJ, Martin DA, Inkeles SB. Role of diet and exercise in the management of hyperinsulinemia and associated atherosclerotic risk factors. Am J Cardiol. 1992;69:440–4.
3. Miyatake N, Nishikawa H, Morishita A, Kunitomi M, Wada J, Suzuki H, et al. Daily walking reduces visceral adipose tissue areas and improves insulin resistance in Japanese obese subjects. Diabetes Res Clin Pract. 2002;58:101–7.
4. Yamanouchi K, Shinozaki T, Chikada K, Nishikawa T, Ito K, Shimizu S, et al. Daily walking combined with diet therapy is a useful means for obese NIDDM patients not only to reduce body weight but also to improve insulin sensitivity. Diabetes Care. 1995;18:775–8.
5. Ohida Y, Yamanouchi K, Hayamizu S, Sato Y. Long-term mild jogging increases insulin action despite no influence on body mass index or VO_2 max. J Appl Physiol. 1989;66:2206–10.
6. National Nutrition Survey in Japan. Available at: http://www.mhlw.go.jp/houdou/2008/12/dl/h1225-5i.pdf. Accessed 5 April 2010.
7. Exercise and Physical Activity Reference Quantity for Health Promotion 2006 (EPARQ2006). Available at: http://www.nih.go.jp/eiken/programs/pdf/epar2006.pdf. Accessed 5 April 2010.
8. Wasserman K, Whipp BJ, Koyl SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. J Appl Physiol. 1973;35:236–43.
9. Weber KT, Janicki JS. Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. Am J Cardiol. 1985;55:22–31.
10. Definition and the diagnostic standard for metabolic syndrome—Committee to Evaluate Diagnostic Standards for Metabolic Syndrome (in Japanese). Nippon Naika Gakkai Zasshi. 2005;94:794–809.
11. Miyatake N, Nonaka K, Fujii M. A new air displacement plethysmograph for the determination of Japanese body composition. Diabetes Obes Metab. 1999;1:347–51.
12. Mccrory MA, Gomez TD, Bernauer EM, Mole PA. Evaluation of a new air displacement plethysmograph for measuring human body composition. Med Sci Sports Exerc. 1995;27:1686–91.
13. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. Am Rev Respir Dis. 1985;131:700–8.
14. Davis JA, Frank MH, Whipp BJ, Wasserman K. Anaerobic threshold alterations caused by endurance training in middle-aged men. J Appl Physiol. 1979;46:1039–46.
15. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol. 1986;60:2020–7.
16. Ohta T, Zhang J, Ishikawa K, Tabata I, Yoshitake Y, Miyashita M. Peak oxygen uptake, ventilatory threshold and leg extension power in apparently healthy Japanese (in Japanese). Nippon Koshu Eisei Zasshi. 1999;46:289–97.
17. Miyatake N, Miyachi M, Tabata I, Numata T. Body fat percentage measured by dual energy X-ray absorptiometry is associated with maximal oxygen uptake in Japanese. Anti Aging Med. 2009;6:41–5.
18. Sanada K, Kuchiki T, Miyachi M, McGrath K, Higuchi M, Ebashi H. Effect of age on ventilatory threshold and peak oxygen uptake normalized for regional skeletal mass in Japanese men and women aged 20–80 years. Eur J Appl Physiol. 2006;99:475–83.
19. Miura K. Ventilatory threshold in Japanese-as the basis for exercise prescription for health promotion (in Japanese). Nippon Koshu Eisei Zasshi. 1996;43:220–30.
20. National Nutrition Survey in Japan. Available at: http://www.mhlw.go.jp/houdou/2008/04/dl/h0430-2g.pdf. Accessed 5 April 2010.
21. Zhang JG, Ohta T, Ishikawa-Takata K, Tabata I, Miyashita M. Effects of daily activity by pedometer on peak oxygen consumption (VO_2 peak), ventilator threshold and leg extension power in 30- to 69-year-old Japanese without exercise habit. Eur J Appl Physiol. 2003;90:109–13.
22. Sandvik L, Erikssen J, Thaulow E, Erikssen G, Mundal R, Rodahl K. Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. N Engl J Med. 1993;25:533–7.
23. Watanabe K, Nakadomo F, Maeda K. Relationship between body composition and cardiorespiratory fitness in Japanese junior high school boys and girls. Ann Physiol Anthropol. 1994;13:167–74.

24. Drinkard B, McDuffie J, McCann S, Uwaifo GI, Nicholson J, Yanovski JA. Relationship between walk/run performance and cardiorespiratory fitness in adolescents who are overweight. Phys Ther. 2001;81:1889–96.

25. Andersen LB, Haraldsdottir J. Maximal oxygen uptake, maximal voluntary isometric contraction and physical activity in young Danish adults. Eur J Appl Physiol Occup Physiol. 1993;67: 315–20.

Original Article

Attenuated Age-Related Carotid Arterial Remodeling in Adults with a High Level of Cardiorespiratory Fitness

Yuko Gando[1,2], Kenta Yamamoto[2], Hiroshi Kawano[3], Haruka Murakami[2], Yumi Ohmori[2], Ryoko Kawakami[2], Kiyoshi Sanada[4], Mitsuru Higuchi[3], Izumi Tabata[2,4], and Motohiko Miyachi[2]

[1]Sport Science Research Center, Waseda University, Saitama, Japan
[2]Health Promotion and Exercise Program, National Institute of Health and Nutrition, Tokyo, Japan
[3]Faculty of Sport Sciences, Waseda University, Saitama, Japan
[4]College of Sport and Health Science, Ritsumeikan University, Shiga, Japan

Aim: Cardiorespiratory fitness (CRF) is independently associated with a reduced risk of cardiovascular disease. Carotid arterial remodeling, which is derived from the interplay between carotid luminal dilation and wall thickening, is also an independent predictor of cardiovascular events. We hypothesized that high CRF may be associated with reduced age-related carotid arterial remodeling. This cross-sectional study was performed to determine the relationships between CRF and age-related luminal dilation and wall thickening.

Methods: A total of 771 adults (180 men and 591 women), under age 40 (young), 40-59 (middle-aged), and over age 60 (older) participated in this study. Subjects in each age category were divided into either high (fit) or low (unfit) CRF groups based on $\dot{V}O_{2peak}$. Carotid artery intima-media thickness (IMT) and lumen diameter were measured on ultrasound images. Carotid wall mass was calculated as $\rho L(\pi Re^2\text{-}Ri^2)$.

Results: Two-way ANOVA indicated a significant interaction ($p<0.01$) between age and CRF in determining IMT, lumen diameter, and wall mass. In older subjects, IMT, lumen diameter, and wall mass were significantly lower ($p<0.05$) in the fit than in the unfit group (IMT, 0.69 ± 0.01 vs. 0.74 ± 0.01 mm; lumen diameter, 5.99 ± 0.06 vs. 6.28 ± 0.06 mm; wall mass, 7.41 ± 0.25 vs. 8.71 ± 0.25 mm^3). Multiple regression analysis indicated that the value of $\dot{V}O_{2peak}$ was independently correlated with carotid IMT, lumen diameter and wall mass.

Conclusion: The present study indicated that a high level of CRF is associated with reduced age-related wall thickening and luminal dilation in the carotid artery.

J Atheroscler Thromb, 2011; 18:248-254.

Key words; Aging, Fitness, Intima-media thickness, Lumen diameter, Remodeling

Introduction

Elastic arteries undergo remodeling with advancing age (intimal and medial thickening[1]) and luminal dilation[2]). Arterial remodeling is usually an adaptive process that occurs in response to long-term changes in hemodynamic conditions, but may subsequently contribute to the pathophysiology of vascular diseases and circulatory disorders.

Carotid artery intima-media thickness (IMT) is an independent risk factor for cardiovascular disease (CVD)[3,4]. On the other hand, cardiorespiratory fitness (CRF) is independently associated with a reduced risk of CVD[5,6]. Thus, many previous studies focused mainly on the relationships between the CRF level and the age-related increase in carotid IMT. In addition to carotid IMT, carotid arterial remodeling derived from the interplay between carotid luminal dilation and wall thickening[7] is an independent predictor of cardiovascular events[8]. Previous studies sug-

Address for correspondence: Yuko Gando, Waseda University Sport Science Research Center, 2-579-15, Mikajima, Tokorozawa, Saitama, 359-1192, Japan
E-mail: gando-y@moegi.waseda.jp
Received: August 26, 2010
Accepted for publication: October 26, 2010

Table 1. Subject characteristics divided by age and fitness groups

	Young		Middle-aged		Older	
	Fit	Unfit	Fit	Unfit	Fit	Unfit
N	135	135	170	170	80	81
Men/Women, n	38/97	38/97	41/129	41/129	11/69	11/70
Age, years	28 ± 1	28 ± 1	50 ± 1*	51 ± 1*	63 ± 1*‡	64 ± 1*‡
Height, cm	164.2 ± 0.6	163.9 ± 0.7	160.0 ± 0.6*	160.1 ± 0.6*	156.9 ± 0.7*‡	156.9 ± 0.7*‡
Weight, kg	59.0 ± 0.9	59.3 ± 1.1	57.8 ± 0.8	61.7 ± 0.7†	54.2 ± 0.9*‡	55.9 ± 0.9‡
BMI, kg/m^2	21.6 ± 0.2	21.9 ± 0.3	22.4 ± 0.2*	24.1 ± 0.3*†	21.9 ± 0.3	22.6 ± 0.3‡
Body Fat, %	20.1 ± 0.4	24.8 ± 0.4†	23.9 ± 0.4*	30.4 ± 0.5*†	26.7 ± 0.6*	29.9 ± 0.5*†
SBP, mmHg	109 ± 1	109 ± 1	118 ± 1*	119 ± 1*	120 ± 2*	127 ± 2*‡†
DBP, mmHg	63 ± 1	64 ± 1	72 ± 1*	72 ± 1*	71 ± 1*	74 ± 1*
MAP, mmHg	81 ± 1	81 ± 1	91 ± 1*	91 ± 1*	92 ± 1*	97 ± 2*‡†
Carotid SBP, mmHg	102 ± 1	101 ± 1	117 ± 2*	118 ± 2*	121 ± 3*	131 ± 3*‡†
Plasma glucose, mmol/L	4.8 ± 0.1	4.8 ± 0.1	5.0 ± 0.1*	5.1 ± 0.1*†	5.2 ± 0.1*‡	5.3 ± 0.1*‡
Plasma insulin, μU/mL	5.1 ± 0.2	5.4 ± 0.2	4.1 ± 0.2*	5.0 ± 0.2†	4.3 ± 0.3	5.2 ± 0.5
Total cholesterol, mmol/L	4.55 ± 0.07	4.66 ± 0.06	5.39 ± 0.07*	5.39 ± 0.07*	5.78 ± 0.08*‡	5.80 ± 0.09*‡
HDL cholesterol, mmol/L	1.70 ± 0.03	1.58 ± 0.03†	1.76 ± 0.03	1.58 ± 0.03†	1.73 ± 0.04	1.64 ± 0.04
Triglycerides, mmol/L	0.72 ± 0.03	0.83 ± 0.04†	0.91 ± 0.04*	1.09 ± 0.05*†	0.95 ± 0.04*	1.04 ± 0.05*
LDL cholesterol, mmol/L	2.70 ± 0.06	2.91 ± 0.06†	3.44 ± 0.06*	3.59 ± 0.06*	3.86 ± 0.08*‡	3.95 ± 0.06*‡
$\dot{V}O_{2peak}$, mL/kg per min	41.1 ± 0.40	31.9 ± 0.3†	35.4 ± 0.4*	26.0 ± 0.3*†	32.2 ± 0.5*‡	23.7 ± 0.4*‡†

Data are the means ± SE. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; $\dot{V}O_{2peak}$, peak oxygen uptake.
*$p<0.05$ vs. young subjects within the same fitness group; ‡$p<0.05$ vs. middle-aged subjects within the same fitness group; †$p<0.05$ vs. fit subjects within the same age category.

gested that dilation of the lumen diameter is a typical vascular profile in patients with long-standing hypertension[9, 10] and may reflect the fatiguing effects of repeated intense cyclic stress[11]. Increased carotid wall mass according to luminal dilation and/or wall thickening is associated with an increased risk of cardiovascular events[8]. Thus, when considering the pathophysiological implications of vascular disease, it is also important not to overlook changes in both age-related carotid luminal dilation and wall thickening (arterial remodeling); however, the associations between the CRF level and age-related carotid arterial remodeling have attracted relatively little attention.

Accordingly, the primary aim of the present cross-sectional study was to determine the relationships between CRF and age-related carotid arterial remodeling. We hypothesized that higher CRF would be associated with reduced age-related carotid arterial remodeling.

Methods

Subjects

A total of 771 adults (180 men and 591 women), under the age of 40 (young), 40-59 years of age (middle-aged), and over the age of 60 (older) participated in this study (**Table 1**). None of the subjects smoked or were on medication for hypertension, hyperlipidemia, or diabetes. Subjects with a history of stroke, cardiac disease, chronic renal failure, or peripheral arterial disease, as well as those who regularly engaged in weight training, were excluded from the study[12]. Subjects who demonstrated significant IMT (>1.5 mm), plaque formation[13], ankle-brachial pressure index <0.90, and/or characteristics of atherosclerosis were excluded. Before testing, subjects abstained from caffeine and fasted for at least 4 hours (10-h overnight fast was used to determine metabolic risk factors and blood pressure (BP)). The purpose, procedures, and risks of the study were explained to each participant prior to inclusion, and all subjects gave their written informed consent before participating in the study, which was approved by the Human Research Committee of the National Institute of Health and Nutrition. The study was performed in accordance with the guidelines of the Declaration of Helsinki.

Carotid Artery IMT, Lumen Diameter, and Wall Mass

Carotid artery IMT and lumen diameter were

measured from ultrasound images (vivid i; GE Medical System) equipped with a high-resolution linear array transducer, as described previously[14, 15]. Longitudinal two-dimensional ultrasound images were obtained at the proximal 1- to 2-cm straight portion of the common carotid artery. These images were first recorded on an ultrasound machine for later offline analysis, and then stored on hard disk. Carotid images were obtained by two trained investigators.

Ultrasound carotid images were analyzed using Image J image analysis software (National Institutes of Health, Bethesda, MD). Carotid IMT was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface[14]. Carotid lumen diameter was defined as the distance between the lumen and intima, and a near-wall boundary, corresponding to the interface of the adventitia and media. These measurements were made at end diastole, as described previously[14]. At least 10 measurements of IMT and lumen diameter were taken in each segment. The mean values of these 10 measurements were used for analysis. Carotid wall mass was calculated, as previously reported[16], as $\rho L(\pi Re^2\text{-}Ri^2)$, where ρ is the arterial wall density ($\rho = 1.06$)[17], L is the length of the arterial segment (L=1 cm), and Re and Ri are the mean external and internal radii, respectively. Image analyses were performed by two investigators blinded to the group assignment of the subjects. Intraobserver and interobserver variabilities of measurements were examined in 100 subjects. Intraobserver and interobserver variabilities of measurements were 3.7% and 4.2% for carotid IMT and 2.0% and 2.2% for the lumen diameter, respectively.

Carotid Arterial Blood Pressure

The pressure waveform and amplitude were obtained from the common carotid artery with a vascular testing device (PWV/ABI; Omron Colin, Kyoto, Japan). A multielement tonometry sensor, consisting of 15 pressure-sensitive small elements aligned side by side, was coupled to the device. The carotid tonometry sensor is compact and lightweight and can be easily attached around the neck. The sensor element, located manually at the center of the carotid artery, can be identified by screening the pulse pressure (PP) levels of the 15 elements provided that the sensor element is sufficiently small compared with the vessel diameter. The quality of the carotid pulse wave and the downward force were checked visually by carotid compression tonography, and pulse waves were recorded and stored over periods of 30 s. As baseline levels of BP are subjected to hold-down force, the pressure signal obtained by tonometry was calibrated by equating the carotid mean arterial pressure (MAP) and diastolic blood pressure (DBP) to the brachial artery value[18]. Intraobserver variability of measurements was 4.0% for carotid systolic blood pressure (SBP).

Brachial Arterial Bold Pressure

Brachial BP was measured with an oscillometric device (PWV/ABI; Omron Colin) with subjects in the supine position. All measurements conformed to the American Heart Association Guidelines[19].

Cardiorespiratory Fitness

CRF, assessed from peak oxygen uptake ($\dot{V}O_{2peak}$), was measured by an incremental cycle exercise test using a cycle ergometer (Ergomedic 828E Test Cycle; Monark, Varberg, Sweden) as described previously[20, 21]. To assess the effects of CRF on carotid IMT, the subjects were categorized into high (fit) or low (unfit) CRF groups on the basis of the median value of $\dot{V}O_{2peak}$ in every decade of age in each sex.

Blood Samples

Blood samples were taken after an overnight fast of at least 10 h to determine fasting glucose and insulin levels. In the same session, serum samples were obtained to determine fasting total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol) and triglyceride levels.

Statistical Analyses

The data were analyzed by two-way ANOVA (age × fitness level) and ANCOVA, which included sex, brachial SBP and body fat as a covariate. In cases with a significant F value, a *post hoc* test with Scheffe's method was used to identify significant differences among mean values. Univariate regression and correlation analyses were used to analyze the relationships between variables of interest. Stepwise multiple regression analysis was used to determine the independent relations of several variables to arterial remodeling values. $P<0.05$ was considered significant. Data are presented as the mean ± SE.

Results

Table 1 shows the characteristics of the subjects. Age was associated with shorter stature, greater body fat, and higher blood pressure. The percent body fat value was lower in the fit group than in the unfit group at all ages.

Table 2 shows the effects of age and CRF on

Table 2. Arterial properties divided by age and fitness groups

	Young		Middle-aged		Older	
	Fit	Unfit	Fit	Unfit	Fit	Unfit
IMT, mm	0.56 ± 0.01	0.55 ± 0.01	0.66 ± 0.01*	0.65 ± 0.01*	0.69 ± 0.01*‡	0.74 ± 0.01*‡†
Lumen diameter, mm	5.88 ± 0.04	5.85 ± 0.04	5.85 ± 0.05	6.03 ± 0.05*†	5.99 ± 0.06	6.28 ± 0.06*‡†
Wall mass, mm^3	5.88 ± 0.12	5.73 ± 0.14	6.76 ± 0.16*	7.06 ± 0.15*	7.41 ± 0.25*‡	8.71 ± 0.25*‡†

Data are the means ± SE. IMT, intima-media thickness; *$p < 0.05$ vs. young subjects within the same fitness group; ‡$p < 0.05$ vs. middle-aged subjects within the same fitness group; †$p < 0.05$ vs. fit subjects within the same age category.

carotid IMT, lumen diameter, and wall mass. Two-way ANOVA indicated a significant interaction ($p < 0.01$) between age and CRF in determining carotid IMT, lumen diameter, and wall mass. Carotid IMT and wall mass increased progressively with age in both fitness groups. Lumen diameter increased progressively with age in the unfit group but was not different at any age in the fit group. Carotid IMT and wall mass were lower ($p < 0.05$) in fit than in unfit older subjects and lumen diameter was lower ($p < 0.05$) in fit than in unfit middle-aged and older subjects. In the older group, these differences remained significant after normalizing for sex, brachial SBP and body fat as covariates; however, in the middle-aged group, the differences were abolished after normalizing for sex, brachial SBP and body fat. **Fig. 1** shows the relationships between $\dot{V}O_{2peak}$ and carotid IMT (A), lumen diameter (B), and wall mass (C) in each age category. Carotid IMT ($r = -0.24$, $p < 0.05$), luminal diameter ($r = -0.28$, $p < 0.01$), and wall mass ($r = -0.30$, $p < 0.01$) were correlated with $\dot{V}O_{2peak}$ in older subjects. There were no significant relationships in young or middle-aged subjects.

In older subjects, the analysis also indicated that carotid IMT was correlated with brachial SBP ($r = 0.29$), carotid SBP (0.28), weight (0.13), $\dot{V}O_{2peak}$ (−0.24), and HDL-cholesterol (−0.26). Stepwise multiple regression analysis revealed that brachial SBP ($\beta = 0.24$), HDL-cholesterol (−0.23), and $\dot{V}O_{2peak}$ (−0.16) were independently correlated with carotid IMT.

In older subjects, the analysis also indicated that lumen diameter was correlated with brachial SBP ($r = 0.43$), carotid SBP (0.39), weight (0.36), $\dot{V}O_{2peak}$ (−0.28), plasma glucose (0.24), plasma insulin (0.25), HDL-cholesterol (−0.16), and triglycerides (0.18). Stepwise multiple regression analysis revealed that brachial SBP ($\beta = 0.38$), weight (0.32), and $\dot{V}O_{2peak}$ (−0.16) were independently correlated with lumen diameter.

In older subjects, the analysis also indicated that wall mass was correlated with brachial SBP ($r = 0.45$), carotid SBP (0.41), weight (0.33), $\dot{V}O_{2peak}$ (−0.30), HDL-cholesterol (−0.24), plasma insulin (0.23), plasma glucose (0.19), and triglycerides (0.16). Stepwise multiple regression analysis revealed that brachial SBP ($\beta = 0.42$), weight (0.28), and $\dot{V}O_{2peak}$ (−0.19) were independently correlated with wall mass.

Discussion

The key new findings of the present study were as follows. First, in the older group, carotid IMT, lumen diameter, and wall mass were significantly lower in the fit group than in the unfit group. Second, although carotid IMT and wall mass increased with age in both fitness groups, the magnitude of age-related increases was smaller in the fit group than in the unfit group. Third, carotid lumen diameter increased with advancing age in the unfit group but no differences were observed at any age in the fit group. Fourth, multiple regression analysis revealed that $\dot{V}O_{2peak}$ was independently correlated with carotid IMT, lumen diameter, or wall mass. These results suggested that higher CRF is associated with lower levels of age-related carotid arterial remodeling.

There have been many reports regarding the relationships between age-related increases in carotid IMT and CRF levels; however, these previous studies did not focus on the age-related dilation of the lumen diameter and increases in wall mass, and their findings were inconsistent. Specifically, the CRF level and habitual exercise have been reported to be associated with lower[22-24], no difference[25-27], or even greater[28] carotid IMT. Similar to previous findings by Galetta *et al.*[29], the present study also showed that a high level of CRF is related to an attenuation of age-related carotid arterial remodeling. An advantage of our study was the considerable number of subjects with a wide age range. Moreover, the strength of the present study was that CRF levels of all subjects were evaluated by maximal exercise testing. Considering the emphasis

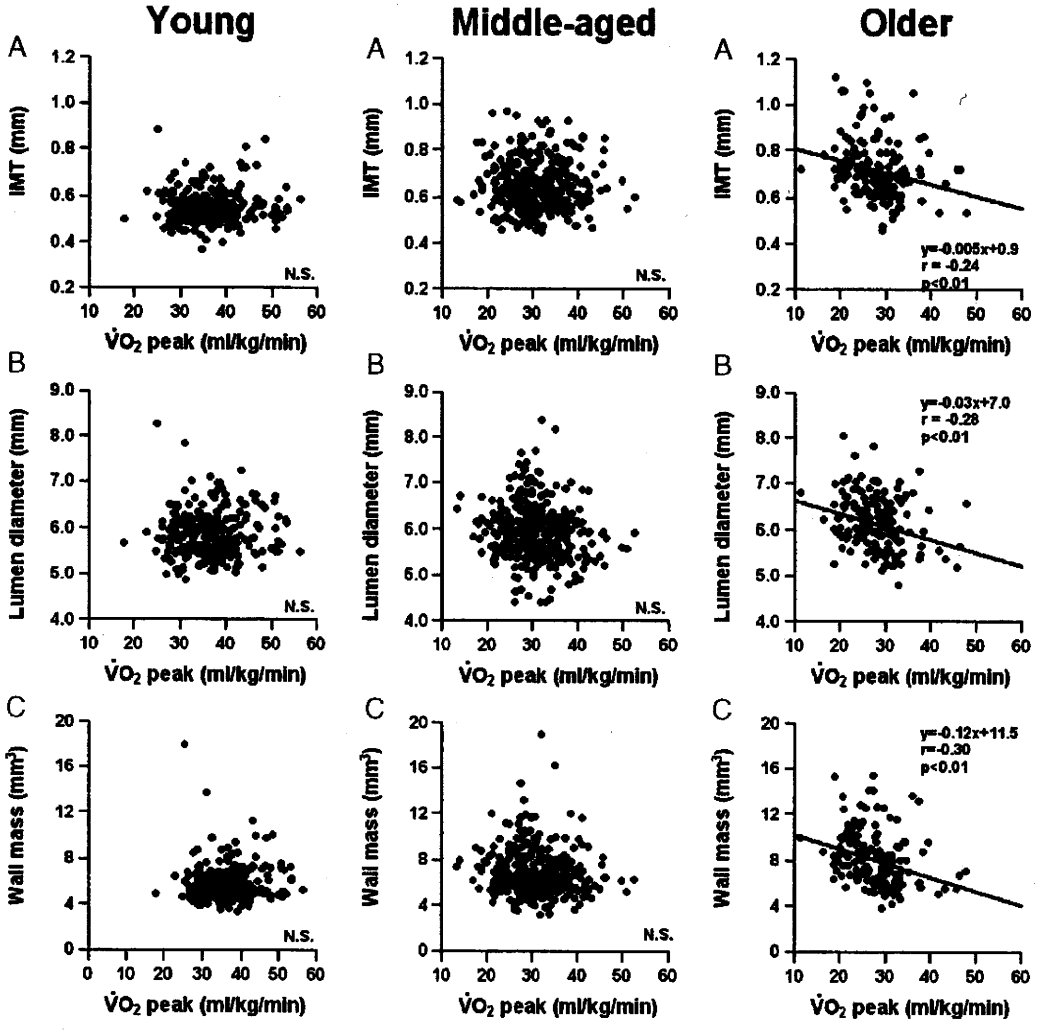

Fig. 1. Relationships between CRF and carotid IMT (A), lumen diameter (B), and wall mass (C) in each age category.

placed on dilation of the lumen diameter and increases in wall mass for prevention of CVD[8], we extended our research to age-related luminal dilation and wall thickening. Similar to some previous reports, the present study also showed that carotid IMT was lower in fit older subjects than in their unfit counterparts. More importantly, the present study demonstrated that lumen diameter and wall mass were lower in fit older subjects than in their unfit counterparts. The present findings suggested that higher CRF is associated with reduced age-related luminal dilation and wall thickening.

We can only speculate on the mechanisms responsible for the attenuation of age-related luminal dilation and wall thickening by higher CRF. Age-related arterial remodeling is primarily an adaptive response of the arterial wall to progressive elevations in chronic arterial BP[30]. The results of animal and human studies indicated that an increase in distending pressure is a major stimulus for hypertrophy of smooth muscle cells and the synthesis of extracellular matrix in the arterial wall[31-34]. Repeated intense cyclic stress may cause fracture of the load-bearing elastin fibers and thus dilation of the lumen[11]. Therefore, we propose that the smaller degree of age-related luminal dilation and increase in wall mass in fit groups may be due to a smaller age-related increase in blood pressure. Indeed, in this study, brachial SBP and carotid SBP were positively associated with carotid IMT, lumen diameter or wall mass in older subjects. However, in a

stepwise multiple regression model that included these factors, $\dot{V}O_{2peak}$ was independently related to carotid IMT, lumen diameter, or wall mass. Park *et al.*[35] reported that wall internal area and wall thickness area of the aorta were increased by menopause and improved by regular exercise in an animal study. As noted by Park *et al.*, eNOS and endothelin-1 in the aorta tissue may participate in these mechanisms. Moreover, the mechanisms by which the maintenance of higher CRF may directly influence lumen diameter and wall mass are still speculative and include the effect of an endurance-trained state on the calcium content[36] and advanced glycation end products and collagen cross-linkage in the arterial wall[37]. Exercise ameliorated the progression of endothelial dysfunction[38] and atherosclerotic lesion formation with a strong negative correlation between atherosclerotic areas and the mean running distance per day[39].

Our findings have a number of important implications. The present study showed that higher CRF was associated with smaller age-related increases in carotid IMT and wall mass and dilation of the lumen. As both luminal dilation and wall thickening are risk factors for CVD[3, 4, 8], the maintenance of higher CRF may have a protective effect against CVD in part by attenuating age-related carotid arterial remodeling; therefore, the improvement of CRF may be important for primary prevention of CVD.

A major limitation of the present study was its cross-sectional design. Due to the design of this study, we could not evaluate individual changes in age-related carotid arterial remodeling. A recent prospective study by Kozakova *et al.*[22] reported that a period of vigorous activity influenced the 3-year IMT progression in a young to middle-aged population (30-60 yr). More research will be needed to determine cause-and-effect relationships in the older population (over 60 yr).

In conclusion, the present study indicated that a high level of CRF is associated with reduced age-related wall thickening and luminal dilation in the carotid artery.

Grants

This study was supported by a Grant-in-Aid for Scientific Research (#20300231, M. Miyachi, #18200041, H. Shibayama) and a Grant-in-Aid for Scientific Research from the Ministry of Health, Labor, and Welfare of Japan (M. Miyachi).

Disclosure

The authors declare no conflicts of interest.

References

1) Nagai Y, Metter EJ, Earley CJ, Kemper MK, Becker LC, Lakatta EG, Fleg JL: Increased carotid artery intimal-medial thickness in asymptomatic older subjects with exercise-induced myocardial ischemia. Circulation, 1998; 98: 1504-1509
2) Lakatta EG: Cardiovascular regulatory mechanisms in advanced age. Physiol Rev, 1993; 73: 413-467
3) Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE: Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation, 1997; 96: 1432-1437
4) O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med, 1999; 340: 14-22
5) Church TS, LaMonte MJ, Barlow CE, Blair SN: Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. Arch Intern Med, 2005; 165: 2114-2120
6) Lee IM, Paffenbarger RS Jr: Physical activity and stroke incidence: the Harvard Alumni Health Study. Stroke, 1998; 29: 2049-2054
7) Scuteri A, Chen CH, Yin FC, Chih-Tai T, Spurgeon HA, Lakatta EG: Functional correlates of central arterial geometric phenotypes. Hypertension, 2001; 38: 1471-1475
8) Scuteri A, Manolio TA, Marino EK, Arnold AM, Lakatta EG: Prevalence of specific variant carotid geometric patterns and incidence of cardiovascular events in older persons. The Cardiovascular Health Study (CHS E-131). J Am Coll Cardiol, 2004; 43: 187-193
9) Mourad JJ, Girerd X, Boutouyrie P, Safar M, Laurent S: Opposite effects of remodeling and hypertrophy on arterial compliance in hypertension. Hypertension, 1998; 31: 529-533
10) Bonithon-Kopp C, Touboul PJ, Berr C, Magne C, Ducimetiere P: Factors of carotid arterial enlargement in a population aged 59 to 71 years: the EVA study. Stroke, 1996; 27: 654-660
11) Reneman RS, van Merode T, Hick P, Hoeks AP: Flow velocity patterns in and distensibility of the carotid artery bulb in subjects of various ages. Circulation, 1985; 71: 500-509
12) Miyachi M, Donato AJ, Yamamoto K, Takahashi K, Gates PE, Moreau KL, Tanaka H: Greater age-related reductions in central arterial compliance in resistance-trained men. Hypertension, 2003; 41: 130-135
13) Homma S, Hirose N, Ishida H, Ishii T, Araki G: Carotid plaque and intima-media thickness assessed by b-mode ultrasonography in subjects ranging from young adults to centenarians. Stroke, 2001; 32: 830-835
14) Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R: Intimal

plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation, 1986; 74: 1399-1406
15) Miyachi M, Kawano H, Sugawara J, Takahashi K, Hayashi K, Yamazaki K, Tabata I, Tanaka H: Unfavorable effects of resistance training on central arterial compliance: a randomized intervention study. Circulation, 2004; 110: 2858-2863
16) Girerd X, Mourad JJ, Copie X, Moulin C, Acar C, Safar M, Laurent S: Noninvasive detection of an increased vascular mass in untreated hypertensive patients. Am J Hypertens, 1994; 7: 1076-1084
17) Manolio TA, Kronmal RA, Burke GL, O'Leary DH, Price TR: Short-term predictors of incident stroke in older adults. The Cardiovascular Health Study. Stroke, 1996; 27: 1479-1486
18) Armentano R, Megnien JL, Simon A, Bellenfant F, Barra J, Levenson J: Effects of hypertension on viscoelasticity of carotid and femoral arteries in humans. Hypertension, 1995; 26: 48-54
19) Perloff D, Grim C, Flack J, Frohlich ED, Hill M, McDonald M, Morgenstern BZ: Human blood pressure determination by sphygmomanometry. Circulation, 1993; 88: 2460-2470
20) Gando Y, Kawano H, Yamamoto K, Sanada K, Tanimoto M, Oh T, Ohmori Y, Miyatani M, Usui C, Takahashi E, Tabata I, Higuchi M, Miyachi M: Age and cardiorespiratory fitness are associated with arterial stiffening and left ventricular remodelling. J Hum Hypertens, 2010; 24: 197-206
21) Gando Y, Yamamoto K, Murakami H, Ohmori Y, Kawakami R, Sanada K, Higuchi M, Tabata I, Miyachi M: Longer time spent in light physical activity is associated with reduced arterial stiffness in older adults. Hypertension, 2010; 56: 540-546
22) Kozakova M, Palombo C, Morizzo C, Nolan JJ, Konrad T, Balkau B: Effect of sedentary behaviour and vigorous physical activity on segment-specific carotid wall thickness and its progression in a healthy population. Eur Heart J, 2010; 31: 1511-1519
23) Folsom AR, Eckfeldt JH, Weitzman S, Ma J, Chambless LE, Barnes RW, Cram KB, Hutchinson RG: Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity. Atherosclerosis Risk in Communities (ARIC) Study Investigators. Stroke, 1994; 25: 66-73
24) Stensland-Bugge E, Bonaa KH, Joakimsen O, Njolstad I: Sex differences in the relationship of risk factors to subclinical carotid atherosclerosis measured 15 years later: the Tromso study. Stroke, 2000; 31: 574-581
25) Rauramaa R, Vaisanen S, Mercuri M, Rankinen T, Penttila I, Bond MG: Association of risk factors and body iron status to carotid atherosclerosis in middle-aged eastern Finnish men. Eur Heart J, 1994; 15: 1020-1027
26) Schmidt-Trucksass AS, Grathwohl D, Frey I, Schmid A, Boragk R, Upmeier C, Keul J, Huonker M: Relation of leisure-time physical activity to structural and functional arterial properties of the common carotid artery in male subjects. Atherosclerosis, 1999; 145: 107-114
27) Tanaka H, Seals DR, Monahan KD, Clevenger CM, DeSouza CA, Dinenno FA: Regular aerobic exercise and the age-related increase in carotid artery intima-media thickness in healthy men. J Appl Physiol, 2002; 92: 1458-1464
28) Cuspidi C, Lonati L, Sampieri L, Leonetti G, Zanchetti A: Similarities and differences in structural and functional changes of left ventricle and carotid arteries in young borderline hypertensives and in athletes. J Hypertens, 1996; 14: 759-764
29) Galetta F, Franzoni F, Virdis A, Ghiadoni L, Taddei S, Salvetti A, Santoro G: Endothelium-dependent vasodilation and carotid artery wall remodeling in athletes and sedentary subjects. Atherosclerosis, 2006; 186: 184-192
30) Boutouyrie P, Bussy C, Lacolley P, Girerd X, Laloux B, Laurent S: Association between local pulse pressure, mean blood pressure, and large-artery remodeling. Circulation, 1999; 100: 1387-1393
31) Leung DY, Glagov S, Mathews MB: Cyclic stretching stimulates synthesis of matrix components by arterial smooth muscle cells in vitro. Science, 1976; 191: 475-477
32) Folkow B: The fourth Volhard lecture: cardiovascular structural adaptation; its role in the initiation and maintenance of primary hypertension. Clin Sci Mol Med Suppl, 1978; 4: 3s-22s
33) Dobrin PB: Mechanical factors associated with the development of intimal and medial thickening in vein grafts subjected to arterial pressure. A model of arteries exposed to hypertension. Hypertension, 1995; 26: 38-43
34) Tanaka H, Dinenno FA, Monahan KD, DeSouza CA, Seals DR: Carotid artery wall hypertrophy with age is related to local systolic blood pressure in healthy men. Arterioscler Thromb Vasc Biol, 2001; 21: 82-87
35) Park JH, Iemitsu M, Maeda S, Kitajima A, Nosaka T, Omi N: Voluntary running exercise attenuates the progression of endothelial dysfunction and arterial calcification in ovariectomized rats. Acta Physiol (Oxf), 2008; 193: 47-55
36) Matsuda M, Nosaka T, Sato M, Ohshima N: Effects of physical exercise on the elasticity and elastic components of the rat aorta. Eur J Appl Physiol Occup Physiol, 1993; 66: 122-126
37) Vaitkevicius PV, Lane M, Spurgeon H, Ingram DK, Roth GS, Egan JJ, Vasan S, Wagle DR, Ulrich P, Brines M, Wuerth JP, Cerami A, Lakatta EG: A cross-link breaker has sustained effects on arterial and ventricular properties in older rhesus monkeys. Proc Natl Acad Sci U S A, 2001; 98: 1171-1175
38) Okada S, Hiuge A, Makino H, Nagumo A, Takaki H, Konishi H, Goto Y, Yoshimasa Y, Miyamoto Y: Effect of exercise intervention on endothelial function and incidence of cardiovascular disease in patients with type 2 diabetes. J Atheroscler Thromb, 2010; 17: 828-833
39) Fukao K, Shimada K, Naito H, Sumiyoshi K, Inoue N, Iesaki T, Kume A, Kiyanagi T, Hiki M, Hirose K, Matsumori R, Ohsaka H, Takahashi Y, Toyoda S, Itoh S, Miyazaki T, Tada N, Daida H: Voluntary Exercise Ameliorates the Progression of Atherosclerotic Lesion Formation via Anti-Inflammatory Effects in Apolipoprotein E-Deficient Mice. J Atheroscler Thromb, 2010; 17: 1226-1236

PPARγ2 C1431T genotype increases metabolic syndrome risk in young men with low cardiorespiratory fitness

Kiyoshi Sanada, Motoyuki Iemitsu, Haruka Murakami, Izumi Tabata, Kenta Yamamoto, Yuko Gando, Katsuhiko Suzuki, Mitsuru Higuchi and Motohiko Miyachi

Physiol. Genomics 43:103-109, 2011. First published 14 December 2010;
doi:10.1152/physiolgenomics.00129.2010

Physiol Genomics 43: 103–109, 2011.
First published December 14, 2010; doi:10.1152/physiolgenomics.00129.2010.

CALL FOR PAPERS | *Functional Analysis of Sequence Variation*

PPARγ2 C1431T genotype increases metabolic syndrome risk in young men with low cardiorespiratory fitness

Kiyoshi Sanada,[1,2] Motoyuki Iemitsu,[1] Haruka Murakami,[3] Izumi Tabata,[1] Kenta Yamamoto,[3] Yuko Gando,[4] Katsuhiko Suzuki,[4] Mitsuru Higuchi,[4] and Motohiko Miyachi[3]

[1]*College of Sport and Health Science, Ritsumeikan University, Shiga;* [2]*Consolidated Research Institute for Advanced Science and Medical Care, Waseda University;* [3]*Health Promotion and Exercise, National Institute of Health and Nutrition, Tokyo; and* [4]*Faculty of Sports Sciences, Waseda University, Tokorozawa, Japan*

Submitted 6 July 2010; accepted in final form 8 December 2010

Sanada K, Iemitsu M, Murakami H, Tabata I, Yamamoto K, Gando Y, Suzuki K, Higuchi M, Miyachi M. PPARγ2 C1431T genotype increases metabolic syndrome risk in young men with low cardiorespiratory fitness. *Physiol Genomics* 43: 103–109, 2011. First published December 14, 2010; doi:10.1152/physiolgenomics.00129.2010.—The peroxisome proliferator-activated receptor gamma 2 (PPARγ2) genotypes are related to obesity and the metabolic syndrome (MetS). A low level of cardiorespiratory fitness is also a strong determining factor in the development of MetS. This cross-sectional study was performed to investigate the influence of the interaction between the PPARγ2 genotype and cardiorespiratory fitness on the risk of MetS. Healthy Japanese men (n = 211) and women (n = 505) participated in this study. All subjects were divided into 8 groups according to sex, fitness level (high and low fitness groups), and age (younger, age < 40 yr; middle-aged/older, age ≥ 40 yr). The PPARγ2 genotypes (Pro12Ala and C1431T) were analyzed by real-time PCR with Taq-Man probes. Two-way ANCOVA with adjustment for age as a covariate indicated that fitness and the CC genotype of C1431T in the PPARγ2 gene interacted to produce a significant effect on MetS risk in younger men and that the risk of MetS in the CC genotype group with low cardiorespiratory fitness was significantly higher than that in the corresponding CT+TT genotypes or in the high fitness groups. There was no significant interaction between fitness and genotype in determining MetS risk in middle-aged/older men or in women in any group. With regard to the Pro12Ala genotype of the PPARγ2 gene, there were no significant differences in fitness or genotype effects nor were there any interactions between measurement variables. We concluded that the CC genotype of C1431T in the PPARγ2 gene together with low cardiorespiratory fitness may increase the risk of MetS in younger men (age < 40 yr), even with adjustment for age.

physical fitness; peroxisome proliferator-activated receptor gamma 2; health care research; maximal oxygen uptake; obesity gene

THERE HAS BEEN A CONSIDERABLE increase in the number of studies reporting associations between DNA sequence variation in specific genes and obesity phenotypes (41). One such gene, that for peroxisome proliferator-activated receptor gamma 2 (PPARγ2), is reported to be associated with metabolic syndrome (MetS) or adipocytokine dysregulation (37, 52–53). Two common polymorphisms, a proline (Pro)-to-alanine (Ala) substitution located at codon 12 (Pro12Ala)(54) and a synonymous C-to-T substitution in exon 6 at nucleotide 1431 (C1431T)(30), have been associated with a reduced risk for the development of diabetes (33), a low adiponectin concentration (45), and an exercise-mediated change in insulin resistance (18) in Japanese people. The protective effect of the Ala allele of Pro12Ala against Type 2 diabetes has been replicated in Japanese, Caucasian-American, Finnish, and Danish populations; however, a deleterious effect of this allele on Type 2 diabetes has been demonstrated in Canadians, Germans, and obese Finns (28). Conversely, the CT+TT genotypes of C1431T in the PPARγ2 gene in Scotland (7) and in Greek children (22) are associated with increases in body mass index (BMI) and waist circumference compared with the CC genotype and are associated with a reduced risk for MetS in 647 Caucasian-Australian patients (26). However, some investigators have shown that the C1431T variant by itself is not associated with BMI or risk factors for MetS (14, 35).

Previous studies regarding the relationship between cardiorespiratory fitness and MetS suggested that a low level of physical fitness is a strong determining factor in the prevalence of MetS (6, 11, 23–25, 38, 50), because cardiorespiratory fitness is strongly correlated with physical activity (39). Lakka et al. (23) suggested that a sedentary lifestyle and an especially low cardiorespiratory fitness measured by maximal oxygen uptake ($\dot{V}O_{2max}$) are not only associated with MetS but could also be considered features of MetS. In addition, Lee et al. (25) reported that high levels of cardiorespiratory fitness are associated with a substantial reduction in health risk for a given level of visceral and subcutaneous fat. Therefore, it is important to consider individual cardiorespiratory fitness to clarify the relationship between PPARγ2 genotypes and MetS. The present study was performed to investigate the influence of interaction between the PPARγ2 genotype and cardiorespiratory fitness on the risk of MetS.

METHODS

Subjects. The subjects included in this cross-sectional study were 716 Japanese adults between 18 and 84 yr of age, consisting of 211 men and 505 women, as described previously were the same subjects included in Ref. 32. All subjects were free of any overt signs or symptoms of chronic disease. They were sedentary or moderately active subjects who participated in a swimming, stretching, and "healthy gymnastics" program; however, they did not participate in other vigorous sports activities. All subjects were divided according to sex and age (young < 40 yr old and middle-aged/older ≥ 40 yr old), because metabolic profiles differ according to both sex and age. The

Address for reprint requests and other correspondence: K. Sanada, College of Sport and Health Science, Ritsumeikan Univ., 1-1-1 Noji Higashi, Kusatsu, Shiga 525-8577, Japan (e-mail: ksanada@fc.ritsumei.ac.jp).

purpose, procedures, and risks of the study were explained to each participant prior to enrollment, and all subjects gave their written informed consent before participating in the study, which was approved by the Human Ethical Committee of Waseda University. The study was performed in accordance with the guidelines of the Declaration of Helsinki. Body weight and height were recorded, and BMI was calculated as weight in kilograms divided by the square of the height in meters. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) were measured at rest by using a vascular testing device (Colin Medical Technology, Tokyo, Japan).

Measurements of blood samples. All blood samples were drawn from the subjects in the seated position. Fasting (> 12 h) blood samples were collected by venipuncture in tubes with or without ethylenediamine tetraacetic acid (for plasma or serum). The blood samples were centrifuged at 1,500 rpm for 15 min and stored at −20°C. Serum concentrations of triglycerides were determined by using commercial kits (Mitsubishi Chemical Medience, Tokyo, Japan). Serum high-density lipoprotein (HDL) cholesterol was measured by an enzymatic method (Mitsubishi Chemical Medience). Fasting plasma glucose (FPG) was measured by the glucose dehydrogenase method (21). Whole blood glycohemoglobin A1c (HbA1c) was measured by an enzymatic method (Glycohemoglobin A1c kit; Mitsubishi Chemical Medience). As waist circumference data were not available, the following risk factors of MetS (highest value = 4) were used: *1*) BMI ≥ 25 kg/m^2; *2*) blood pressure ≥ 130 mmHg in systolic and/or ≥ 85 mmHg in diastolic; *3*) triglycerides ≥ 150 mg/dl and/or HDL cholesterol ≤ 40 mg/dl; and *4*) FPG ≥ 110 mg/dl. Moreover, MetS risk (Z-score) was derived by standardizing and then summing the following continuously distributed variables: BMI, MBP, HbA1c, and serum triglyceride/HDL cholesterol, to obtain the Z-score. It is known that a high serum triglycerides/HDL cholesterol ratio is one of the markers of insulin resistance (27). The BMI values can predict the presence of multiple metabolic risk factors similar to waist circumference in middle-aged Japanese subjects (43).

Measurement of $\dot{V}O_{2max}$. The $\dot{V}O_{2max}$ was measured by an incremental cycle exercise test using a cycle ergometer (Monark, Varberg, Sweden) (31). The incremental cycle exercise began at a work rate of 90 W (60 rpm), and power output was increased by 30 W/min until the subjects could not maintain the fixed pedaling frequency. The subjects were encouraged during the ergometer test to exercise at the level of maximum intensity. $\dot{V}O_2$ was monitored during the last 30 s of each increase in work rate. Subjects breathed through a low-resistance two-way valve, and the expired air was collected in Douglas bags. Expired O_2 and CO_2 gas concentrations were measured by mass spectrometry (WSMR-1400; Arco System, Chiba, Japan), and gas volume was determined by using a dry gas meter (NDS-2A-T; Shinagawa Dev., Tokyo, Japan). The highest value of $\dot{V}O_2$ during the exercise test was designated as $\dot{V}O_{2max}$. Moreover, these values were consistent with the reference values for the maximal oxygen uptake for health promotion by sex and age, as described by the Japanese Ministry of Health, Labor, and Welfare to prevent lifestyle-related diseases (12, 17).

Single nucleotide polymorphism genotyping. Genomic DNA was extracted from plasma buffy coats and buccal cells by using a QIAamp DNA Blood Maxi Kit (Qiagen, Tokyo, Japan). Single nucleotide polymorphism (SNP) genotypes were determined by real-time PCR with TaqMan probes using an ABI Prism 7700 Sequence Detector (Perkin-Elmer Applied Biosystems, Foster City, CA) as described previously with minor modifications (16). The gene-specific primers and TaqMan probes for each SNP were synthesized by using Primer Express v. 1.5 software (Perkin-Elmer Applied Biosystems) according to the published DNA sequences for each SNP as follows: Pro12Ala (C>G) in exon 1 of PPARγ2 (NCBI accession ID: rs1805192) and C1431T in exon 6 of PPARγ2 (NCBI accession ID: rs3856806). The sequences of the oligonucleotides used were as follows:

Pro12Ala forward: 5′-GTTATGGGTGAAACTCTGGGAGATT-3′, Pro12Ala reverse: 5′-GCAGACAGTGTATCAGTGAAGGAAT-3′, Pro12Ala/C probe: 5′-CTCCTATTGACCCAGAAAG-3′, Pro12Ala/G probe: 5′-CTATTGACGCAGAAAG-3′, C1431T forward: 5′-CAGAAAATGACAGACCTCAGACAGA-3′, C1431T reverse: 5′-CGTCTTCTTGATCACCTGCAGTAG-3′, C1431T /G probe: 5′-CTGCACGTGTTCCG-3′, C1431T /A probe: 5′-CTGCACATGTTCCG-3′.

PCR 96-well plates were read on an ABI-7700 using the end-point analysis mode of the SDS v. 1.7a software package (Perkin-Elmer Applied Biosystems). Genotypes were determined automatically by the single processing algorithms in the software.

Statistical analysis. The PPARγ2 allelic frequencies were calculated by using a gene-counting method, and Hardy-Weinberg equilibrium was confirmed by performing the χ^2 test. The variables BMI, MBP, HbA1c, and serum triglyceride/HDL cholesterol were standardized to Z-score variables with mean = 0 and standard deviation (SD) = 1 [(individual value − sex and age-specific mean value)/SD]. We tested the influence of genotype and fitness on the risk of MetS by using two-way ANCOVA with adjustment for age as a covariate (genotype and fitness), and when a significant difference was observed in the interaction, comparisons between groups were tested by using the unpaired Student's *t*-test. Regression analyses were conducted to explore the relationship between $\dot{V}O_{2max}$ and MetS risk, excluding variance produced by age by use of partial correlations (partial correlation coefficient). Values were expressed as means ± SE. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

RESULTS

There were no significant differences in the frequencies of C1431T and Pro12Ala polymorphisms between age groups in either sex (Table 1). The genotype frequencies did not deviate from the expected Hardy-Weinberg equilibrium.

Table 1. *Genotype and allele frequencies of the peroxisome proliferator-activated receptor γ2 gene*

			Pro12Ala			C1431T		
			ProPro	ProAla	AlaAla	CC	CT	TT
Women	Age, yr <40	*n* (%)	197 (93.8)	12 (5.7)	1 (0.5)	137 (65.2)	69 (32.9)	4 (1.9)
		MAF		0.033			0.183	
	Age, yr ≥40	*n* (%)	274 (92.9)	20 (6.8)	1 (0.3)	201 (68.1)	84 (28.5)	10 (3.4)
		MAF		0.037			0.176	
Men	Age, yr <40	*n* (%)	86 (93.5)	6 (6.5)	0 (0.0)	73 (79.3)	15 (16.3)	4 (4.3)
		MAF		0.033			0.125	
	Age, yr ≥40	*n* (%)	113 (95.0)	6 (5.0)	0 (0.0)	85 (71.4)	28 (23.5)	6 (5.0)
		MAF		0.025			0.168	

MAF; minor allele frequency. There were no significant differences in the frequencies of C1431T and Pro12Ala polymorphisms between age in both sexes. The allele frequencies did not deviate from the expected Hardy-Weinberg equilibrium.

Significant simple and partial correlations (age-adjusted) were observed between $\dot{V}O_{2max}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) and MetS risk (Z-score) in both men (simple correlation $r = -0.410$, $P < 0.001$, partial correlation $r = -0.371$, $P < 0.001$) and women (simple correlation $r = -0.309$, $P < 0.001$, partial correlation $r = -0.253$, $P < 0.001$); therefore, these findings were independently associated with age.

Neither C1431T nor Pro12Ala was associated with lower BMI regardless of age or sex in healthy Japanese adults. Women with low cardiorespiratory fitness in both age groups and in C1431T genotype groups had a higher BMI than those with high cardiorespiratory fitness ($P < 0.05$), but these associations did not hold for men (Tables 2 and 3). Low cardiorespiratory fitness in younger women of both C1431T genotypes was associated with higher SBP, DBP, and MBP than high cardiorespiratory fitness ($P < 0.05$), but this association was not observed in younger men or in middle-aged/older men and women. The risk of MetS in both C1431T genotypes of younger women with a low level of fitness was significantly higher than that in those with a high level of fitness ($P < 0.01$), but this association was absent in younger men and middle-aged/older people of either sex (Tables 2 and 3, respectively).

The interaction between fitness and genotype significantly affected the risk of MetS in younger men ($P < 0.05$, Fig. 1). Moreover, the MetS risk in low-fitness younger men with the CC genotype in the C1431T polymorphism of the PPARγ2 gene was significantly higher than that in the other groups ($P < 0.05$, Table 2). There was no significant interaction between fitness and genotype in determining MetS risk in middle-aged/older men and younger and middle-aged/older women.

On the other hand, with regard to the Pro12Ala genotype of the PPARγ2 gene, there were no significant differences in fitness or genotype effects nor were there any interactions between measurement variables.

DISCUSSION

A previous study reporting associations between DNA sequence variation in specific genes and obesity phenotypes has increased considerably, with 426 findings of positive associations with 127 candidate genes (41). One of these genes, PPARγ2, which encodes a transcription factor belonging to the nuclear receptor family, is related to lipid metabolism, carbohydrate metabolism, and fatty acid transport (51) and is a candidate gene for susceptibility to obesity and Type 2 diabetes (2, 8, 19, 34). It is directly involved in adipogenesis (46) and muscle responses to glucose (15). A common structural defect has been detected in the PPARγ2 gene, resulting in a Pro-to-Ala substitution (54), located at codon 12 (Pro12Ala); and a

Table 2. *Relationships among cardiorespiratory fitness, C1431T genotype of the peroxisome proliferator-activated receptor γ2 gene, and metabolic syndrome risk in younger subjects (age <40 yr)*

	CC Individuals With Low Fitness	CC Individuals With High Fitness	CT+TT Individuals With Low Fitness	CT+TT Individuals With High Fitness	*P* Genotype	*P* Fitness	*P* Interaction
			Women				
n	46	91	23	50			
Age, yr	26.5 ± 1.0	26.6 ± 0.7	25.0 ± 1.1	24.1 ± 0.8			
Body mass index, kg/m^2	21.6 ± 0.4	20.9 ± 0.2	21.1 ± 0.5	20.7 ± 0.3	0.126	**0.031**	0.968
Systolic blood pressure, mmHg	105.3 ± 1.5	107.4 ± 0.9	103.5 ± 1.7	105.5 ± 0.9	0.353	**0.001**	0.718
Diastolic blood pressure, mmHg	62.1 ± 1.3	61.7 ± 0.7	59.9 ± 1.3	59.5 ± 0.7	0.561	**0.001**	0.847
Mean blood pressure, mmHg	79.1 ± 1.4	79.3 ± 0.8	76.0 ± 1.3	77.0 ± 0.8	0.286	**0.000**	0.965
Serum triglyceride, g/dl	68.7 ± 4.6	57.2 ± 2.4	61.9 ± 4.3	60.3 ± 3.0	0.521	0.683	0.199
HDL cholesterol, mg/dl	66.5 ± 1.9	71.0 ± 1.4	64.7 ± 2.0	69.3 ± 2.0	0.272	0.444	0.976
Serum triglyceride/ HDL cholesterol	1.09 ± 0.09	0.83 ± 0.04	0.99 ± 0.08	0.90 ± 0.05	0.299	0.987	0.185
Fasting plasma glucose, mg/dl	86.9 ± 1.0	86.4 ± 0.6	86.7 ± 1.1	87.0 ± 0.8	0.301	0.459	0.843
HgA1c, %	4.87 ± 0.04	4.80 ± 0.03	4.81 ± 0.06	4.82 ± 0.04	**0.030**	0.749	0.497
Number of MetS risk factors	0.24 ± 0.08	0.07 ± 0.03	0.04 ± 0.04	0.02 ± 0.02	0.281	**0.027**	0.233
MetS risk, Z-score	0.79 ± 0.40	−0.34 ± 0.17	−0.21 ± 0.41	−0.44 ± 0.25	0.078	**0.005**	0.317
Maximal oxygen uptake, $ml \cdot kg^{-1} \cdot min^{-1}$	29.1 ± 0.4	39.2 ± 0.6	29.9 ± 0.4	40.3 ± 0.7	0.276	**0.000**	0.986
			Men				
n	31	42	5	14			
Age, yr	34.8 ± 0.7	27.2 ± 1.0	33.4 ± 2.1	25.5 ± 1.9			
Body mass index, kg/m^2	25.5 ± 0.8	23.2 ± 0.4	22.9 ± 0.6	23.4 ± 0.4	0.446	0.285	0.080
Systolic blood pressure, mmHg	120.7 ± 2.9	116.0 ± 1.6	117.2 ± 1.9	118.4 ± 2.2	0.592	0.890	0.665
Diastolic blood pressure, mmHg	72.9 ± 1.9	64.2 ± 1.3	71.1 ± 2.6	62.3 ± 2.0	0.740	0.649	0.931
Mean blood pressure, mmHg	90.0 ± 2.0	83.5 ± 1.3	86.0 ± 1.8	84.8 ± 1.9	0.940	0.864	0.385
Serum triglyceride, g/dl	111.2 ± 13.4	62.8 ± 3.9	80.0 ± 12.1	80.2 ± 12.6	0.804	0.354	0.138
HDL cholesterol, mg/dl	49.3 ± 1.4	60.7 ± 1.7	56.2 ± 5.5	63.6 ± 3.6	0.274	0.078	0.245
Serum triglyceride/ HDL cholesterol	2.29 ± 0.27	1.09 ± 0.08	1.54 ± 0.33	1.41 ± 0.33	0.565	0.668	0.082
Fasting plasma glucose, mg/dl	90.3 ± 1.2	90.4 ± 1.5	88.6 ± 3.5	92.9 ± 1.3	0.496	0.513	0.277
HgA1c, %	4.79 ± 0.04	4.75 ± 0.04	4.64 ± 0.13	4.76 ± 0.08	0.080	0.686	0.093
Number of MetS risk factors	0.94 ± 0.15	0.33 ± 0.09[a]	0.20 ± 0.20[a]	0.43 ± 0.14[a]	0.421	0.123	**0.023**
MetS risk, Z-score	2.14 ± 0.67	0.53 ± 0.26[a]	−0.27 ± 0.67[a]	0.01 ± 0.65[a]	0.287	0.891	**0.029**
Maximal oxygen uptake, $ml \cdot kg^{-1} \cdot min^{-1}$	33.6 ± 0.6	49.2 ± 1.3	36.5 ± 0.4	52.5 ± 2.8	0.171	**0.000**	0.398

Data are means ± SE unless otherwise indicated. [a]$P < 0.05$ for a significant difference from CC individuals of the C1431T variant with the "low fitness" group using the unpaired Student's *t*-test. *P* values are for significant effects using 2-way ANCOVA with adjustment for the covariate of age (genotype × fitness). Boldface indicates significance ($P < 0.05$).

Table 3. *Relationships among cardiorespiratory fitness, C1431T genotype of the peroxisome proliferator-activated receptor γ2 gene, and metabolic syndrome risk in middle/older subjects (age ≥40 yr)*

	CC Individuals With Low Fitness	CC Individuals With High Fitness	CT+TT Individuals With Low Fitness	CT+TT Individuals With High Fitness	*P* Genotype	*P* Fitness	*P* Interaction
			Women				
n	114	87	56	38			
Age, yr	55.7 ± 0.8	53.7 ± 1.0	57.9 ± 1.2	54.9 ± 1.2			
Body mass index, kg/m^2	23.6 ± 0.3	21.6 ± 0.3	23.8 ± 0.4	21.9 ± 0.4	0.657	**0.002**	0.831
Systolic blood pressure, mmHg	121.8 ± 1.7	117.5 ± 1.6	124.4 ± 2.5	114.7 ± 2.3	0.121	0.133	0.454
Diastolic blood pressure, mmHg	72.6 ± 1.0	70.9 ± 1.1	72.3 ± 1.5	69.3 ± 1.6	0.334	0.061	0.951
Mean blood pressure, mmHg	93.3 ± 1.3	90.2 ± 1.4	94.9 ± 2.0	87.7 ± 1.8	0.454	0.131	0.429
Serum triglyceride, g/dl	96.9 ± 5.1	77.2 ± 3.6	84.0 ± 5.4	78.0 ± 7.3	0.480	0.084	0.345
HDL cholesterol, mg/dl	64.6 ± 1.2	73.1 ± 1.8	66.9 ± 1.5	73.4 ± 3.6	0.060	**0.009**	0.534
Serum triglyceride/ HDL cholesterol	1.62 ± 0.11	1.15 ± 0.08	1.31 ± 0.10	1.23 ± 0.18	0.699	0.077	0.162
Fasting plasma glucose, mg/dl	95.4 ± 1.5	92.0 ± 0.9	95.1 ± 1.8	90.2 ± 1.0	0.540	0.354	0.844
HgA1c, %	5.16 ± 0.06	5.00 ± 0.04	5.17 ± 0.08	5.07 ± 0.05	0.536	0.341	0.376
Number of MetS risk factors	0.82 ± 0.09	0.33 ± 0.07	0.77 ± 0.09	0.40 ± 0.12	0.859	0.211	0.595
MetS risk, Z-score	0.91 ± 0.25	−0.54 ± 0.18	0.89 ± 0.25	−0.45 ± 0.31	0.479	0.325	0.698
Maximal oxygen uptake, ml·kg^{-1}·min^{-1}	24.3 ± 0.4	34.6 ± 0.5	24.4 ± 0.4	33.4 ± 0.7	0.887	**0.000**	0.140
			Men				
n	54	31	22	12			
Age, yr	54.2 ± 1.3	52.9 ± 1.9	54.2 ± 2.2	56.1 ± 2.9			
Body mass index, kg/m^2	25.0 ± 0.3	23.2 ± 0.5	24.7 ± 0.6	24.1 ± 0.7	0.283	0.148	0.163
Systolic blood pressure, mmHg	124.9 ± 2.1	126.6 ± 2.6	129.5 ± 3.2	125.3 ± 4.1	0.666	0.565	0.258
Diastolic blood pressure, mmHg	78.9 ± 1.4	78.4 ± 2.0	78.7 ± 2.1	80.1 ± 3.0	0.657	0.347	0.757
Mean blood pressure, mmHg	96.7 ± 1.9	97.6 ± 2.5	98.3 ± 2.8	95.6 ± 3.6	0.803	0.273	0.401
Serum triglyceride, g/dl	122.3 ± 8.3	111.0 ± 8.9	118.2 ± 14.7	109.6 ± 15.7	0.926	0.414	0.979
HDL cholesterol, mg/dl	55.2 ± 1.7	62.3 ± 1.9	57.3 ± 3.5	59.8 ± 2.5	0.275	0.103	0.260
Serum triglyceride/ HDL cholesterol	2.45 ± 0.21	1.94 ± 0.21	2.29 ± 0.33	1.91 ± 0.30	0.964	0.155	0.856
Fasting plasma glucose, mg/dl	98.4 ± 1.7	93.5 ± 1.4	95.5 ± 3.1	98.7 ± 4.5	0.391	0.482	0.167
HgA1c, %	5.16 ± 0.11	4.87 ± 0.04	5.10 ± 0.13	5.02 ± 0.10	0.522	0.330	0.499
Number of MetS risk factors	1.20 ± 0.14	0.97 ± 0.16	1.41 ± 0.20	1.17 ± 0.24	0.483	0.385	0.996
MetS risk, Z-score	1.21 ± 0.33	−0.16 ± 0.38	1.00 ± 0.52	0.26 ± 0.40	0.991	0.952	0.549
Maximal oxygen uptake, ml·kg^{-1}·min^{-1}	28.9 ± 0.6	39.7 ± 0.7	29.0 ± 0.9	38.1 ± 1.4	0.779	**0.026**	0.463

Data are means ± SE unless otherwise indicated.

synonymous C-to-T substitution in exon 6 has been identified at nucleotide 1431 (C1431T)(30) of this gene. However, the reported associations between increased body mass and BMI with the Pro12Ala genotype are inconsistent, with some studies indicating that the Ala allele is associated with either a higher BMI (3, 19, 29, 47) or a lower one (8–10, 40, 48), while other studies have found no association (13, 34, 42, 44). Kao et al. (19) reported that among overweight individuals (BMI 25–29.9 kg/m^2), the ProAla genotype of PPARγ2 is associated with a higher BMI ($P = 0.02$), waist-to-hip ratio ($P = 0.01$), and waist circumference ($P = 0.04$) in nonobese African-Americans. Our data indicated that neither C1431T nor Pro12Ala variants were associated with a lower BMI regardless of age or sex of the healthy Japanese adults in the study groups.

Moderate and high levels of cardiorespiratory fitness attenuate the risk of all causes of and cardiovascular disease mortality in men with MetS (20). To date, many reports on the relationship between cardiorespiratory fitness and MetS have suggested that low physical fitness is a strong predictor for the presence of MetS (6, 11, 23–25, 38, 50). As cardiorespiratory fitness is closely correlated with physical activity (39), there may be an expectation that physical activity, such as cardiorespiratory fitness, would be related to health risk independently of abdominal obesity (25). However, the value of cardiorespiratory fitness in prevention of MetS has not been confirmed. Lakka et al. (23) reported that men with a $\dot{V}o_{2max}$ < 29.1 ml·kg^{-1}·min^{-1} were almost seven times more likely to have MetS than those with a $\dot{V}o_{2max} \geq 35.5$ ml·kg^{-1}·min^{-1} even after adjusting for confounding variables. In this study, significant partial correlations were observed between $\dot{V}o_{2max}$ (ml·kg^{-1}·min^{-1}) and MetS risk in both men and women, even after adjustment for age; and the $\dot{V}o_{2max}$ that corresponded to a MetS risk factor of 1 was shown to be 31.9 ml·kg^{-1}·min^{-1} for men and 21.0·kg^{-1}·min^{-1} for women, as determined by linear regression. These results suggest that low cardiorespiratory fitness was associated with MetS risk independent of age and that cardiorespiratory fitness levels corresponding to this risk may be used as target fitness values for prevention of MetS in Japanese adults.

At present, it is unclear which of the two contributions to MetS is more important: the PPARγ2 genotype or cardiorespiratory fitness. In the present study, the subjects were classified into high- and low-fitness groups according to the criteria issued by the Ministry of Health, Labor, and Welfare of Japan (17). We examined the relationship between the fitness level and PPARγ2 genotype, when the subjects were divided based on their sex and age. The results of this study indicated that younger men with low levels of fitness and the CC genotype of C1431T possessed more risk factors for MetS than those subjects with high fitness levels and the CT+TT genotypes, even after adjustment for age (Table 2 and Fig. 1). These results, therefore, suggest that in younger men (age < 40 yr) with the CC genotype of C1431T and low cardiorespiratory fitness, these factors increase the risk of MetS.

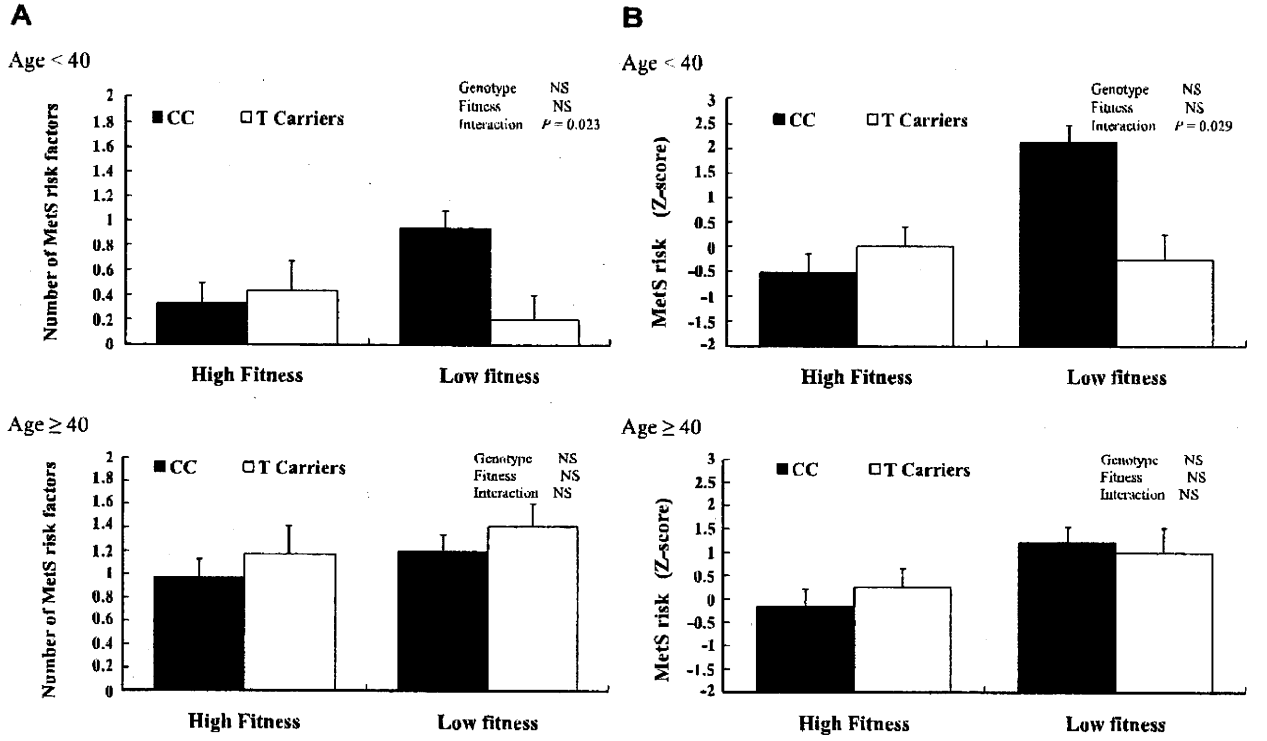

Fig. 1. Interaction between cardiorespiratory fitness and peroxisome proliferator-activated receptor γ2 gene genotype (C1431T) with respect to the number of MetS risk factors (*A*) and MetS risk or Z-score (*B*) in men divided into 2 age groups (age < 40 yr and age ≥ 40 yr). Genotype and fitness effects and interaction (genotype × fitness) were assessed by 2-way ANCOVA with adjustment for age as a covariate. Data are expressed as means ± SE. NS, not significant.

On the other hand, cardiovascular fitness itself is influenced not only by environmental factors such as daily physical activity but also by genetic factors. Bouchard et al. (4) reported a heritability estimate of ~50%, which was correlated with $\dot{V}O_{2max}$ in various parent-offspring and sibling relations, but not among the spouses. In the present study, there were no significant differences in $\dot{V}O_{2max}$ between the CC genotype and CT+TT genotypes of C1431T in the PPARγ2 gene in any of the groups (data not shown). Furthermore, in the human gene map for performance and health-related fitness phenotypes, the fitness and performance map now includes 214 autosomal gene entries and quantitative trait loci plus seven others on the X chromosome (5), but the PPARγ2 genotype is not included in these association studies with candidate genes. Therefore, the CC genotype of C1431T in PPARγ2 affects the relationship between cardiorespiratory fitness and MetS risk but does not separately affect each phenotype. One of the most interesting findings of the present study is that the CC genotype of C1431T in PPARγ2 in younger men, present in 79.3% of the subjects, was associated with MetS risk. These findings indicate that to prevent MetS, it is important to maintain high cardiorespiratory fitness in young male subjects with this genotype.

Some case-control studies have reported evidence of associations between the Pro12Ala genotype in PPARγ2 and responses of glucose and insulin metabolism phenotypes to habitual physical activity or regular exercise (1, 18, 36, 49). However, in the Pro12Ala variant of the PPARγ2 gene, there were no significant differences in fitness or genotype effects nor were there any interactions between measured variables as determined by two-way ANCOVA in this study. Thus, the lower allele frequency for the Ala12 variant in Japanese (2–4%)(33, 45) compared with Europeans and North Americans (14–16%)(2, 10) may have affected these results.

In the present study, the interaction between fitness and genotype significantly affected the MetS risk in younger men, but not in younger women. Younger women in this study had fewer MetS risk factors than younger men, and therefore this effect of PPARγ2 polymorphism may be attenuated in women. However, in middle-aged/older subjects, no interaction between fitness and genotype was observed for either sex. An environmental factor with long-term exposure may participate in attenuation of the genetic factors. Additionally, the interpretation of the observations made in this cross-sectional study must be partly tempered due to the small sample size obtained when the subjects were divided based on their sex, age, fitness, and genotypes. Further study will be necessary using larger numbers of samples, and an intervention study should also be performed.

In conclusion, we found that low cardiorespiratory fitness was associated with MetS risk independent of age and that the CC genotype of C1431T in the PPARγ2 gene associated with low cardiorespiratory fitness increased the risk of MetS in younger men (age < 40 yr), even if these factors were adjusted for age.

GRANTS

This study was partly supported by funding from the program Establishment of Consolidated Research Institute for Advanced Science and Medical Care (K. Sanada); the Encouraging Development Strategic Research Centers

Program; Special Coordination Funds for Promoting Science and Technology (K. Sanada); a grant-in-aid (no. 21300258) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (K. Sanada); the Uehara Memorial Foundation of Japan (M. Iemitsu); and a grant-in-aid for scientific research from the Ministry of Health, Labor, and Welfare of Japan (M. Miyachi).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES

1. **Adamo KB, Sigal RJ, Williams K, Kenny G, Prud'homme D, Tesson F.** Influence of Pro12Ala peroxisome proliferator-activated receptor gamma2 polymorphism on glucose response to exercise training in type 2 diabetes. *Diabetologia* 48: 1503–1509, 2005.
2. **Altshuler D, Hirschhorn JN, Klannemark M, Lindgren CM, Vohl MC, Nemesh J, Lane CR, Schaffner SF, Bolk S, Brewer C, Tuomi T, Gaudet D, Hudson TJ, Daly M, Groop L, Lander ES.** The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet* 26: 76–80, 2000.
3. **Beamer BA, Yen CJ, Andersen RE, Muller D, Elahi D, Cheskin LJ, Andres R, Roth J, Shuldiner AR.** Association of the Pro12Ala variant in the peroxisome proliferator-activated receptor-gamma2 gene with obesity in two Caucasian populations. *Diabetes* 47: 1806–1808, 1998.
4. **Bouchard C, Daw EW, Rice T, Perusse L, Gagnon J, Province MA, Leon AS, Rao DC, Skinner JS, Wilmore JH.** Familial resemblance for VO2max in the sedentary state: the HERITAGE family study. *Med Sci Sports Exerc* 30: 252–258, 1998.
5. **Bray MS, Hagberg JM, Perusse L, Rankinen T, Roth SM, Wolfarth B, Bouchard C.** The human gene map for performance and health-related fitness phenotypes: the 2006–2007 update. *Med Sci Sports Exerc* 41: 35–73, 2009.
6. **Carroll S, Cooke CB, Butterly RJ.** Metabolic clustering, physical activity and fitness in nonsmoking, middle-aged men. *Med Sci Sports Exerc* 32: 2079–2086, 2000.
7. **Cecil JE, Watt P, Palmer CN, Hetherington M.** Energy balance and food intake: the role of PPARgamma gene polymorphisms. *Physiol Behav* 88: 227–233, 2006.
8. **Deeb SS, Fajas L, Nemoto M, Pihlajamaki J, Mykkanen L, Kuusisto J, Laakso M, Fujimoto W, Auwerx J.** A Pro12Ala substitution in PPARgamma2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. *Nat Genet* 20: 284–287, 1998.
9. **Doney A, Fischer B, Frew D, Cumming A, Flavell DM, World M, Montgomery HE, Boyle D, Morris A, Palmer CN.** Haplotype analysis of the PPARgamma Pro12Ala and C1431T variants reveals opposing associations with body weight. *BMC Genet* 3: 21, 2002.
10. **Ek J, Urhammer SA, Sorensen TI, Andersen T, Auwerx J, Pedersen O.** Homozygosity of the Pro12Ala variant of the peroxisome proliferation-activated receptor-gamma2 (PPAR-gamma2): divergent modulating effects on body mass index in obese and lean Caucasian men. *Diabetologia* 42: 892–895, 1999.
11. **Finley CE, LaMonte MJ, Waslien CI, Barlow CE, Blair SN, Nichaman MZ.** Cardiorespiratory fitness, macronutrient intake, and the metabolic syndrome: the Aerobics Center Longitudinal Study. *J Am Diet Assoc* 106: 673–679, 2006.
12. **Gando Y, Kawano H, Yamamoto K, Sanada K, Tanimoto M, Oh T, Ohmori Y, Miyatani M, Usui C, Takahashi E, Tabata I, Higuchi M, Miyachi M.** Age and cardiorespiratory fitness are associated with arterial stiffening and left ventricular remodelling. *J Hum Hypertens* 24: 197–206, 2010.
13. **Hamann A, Munzberg H, Buttron P, Busing B, Hinney A, Mayer H, Siegfried W, Hebebrand J, Greten H.** Missense variants in the human peroxisome proliferator-activated receptor-gamma2 gene in lean and obese subjects. *Eur J Endocrinol* 141: 90–92, 1999.
14. **Haseeb A, Iliyas M, Chakrabarti S, Farooqui AA, Naik SR, Ghosh S, Suragani M, Ehtesham NZ.** Single-nucleotide polymorphisms in peroxisome proliferator-activated receptor gamma and their association with plasma levels of resistin and the metabolic syndrome in a South Indian population. *J Biosci* 34: 405–414, 2009.
15. **Hevener AL, He W, Barak Y, Le J, Bandyopadhyay G, Olson P, Wilkes J, Evans RM, Olefsky J.** Muscle-specific Pparg deletion causes insulin resistance. *Nat Med* 9: 1491–1497, 2003.
16. **Iemitsu M, Maeda S, Otsuki T, Sugawara J, Tanabe T, Jesmin S, Kuno S, Ajisaka R, Miyauchi T, Matsuda M.** Polymorphism in endothelin-related genes limits exercise-induced decreases in arterial stiffness in older subjects. *Hypertension* 47: 928–936, 2006.
17. **Ishikawa-Takata K, Tabata I.** Exercise and Physical Activity Reference for Health Promotion 2006 (EPAR2006). *J Epidemiol* 17: 177, 2007.
18. **Kahara T, Takamura T, Hayakawa T, Nagai Y, Yamaguchi H, Katsuki T, Katsuki K, Katsuki M, Kobayashi K.** PPARgamma gene polymorphism is associated with exercise-mediated changes of insulin resistance in healthy men. *Metabolism* 52: 209–212, 2003.
19. **Kao WH, Coresh J, Shuldiner AR, Boerwinkle E, Bray MS, Brancati FL.** Pro12Ala of the peroxisome proliferator-activated receptor-gamma2 gene is associated with lower serum insulin levels in nonobese African Americans: the Atherosclerosis Risk in Communities Study. *Diabetes* 52: 1568–1572, 2003.
20. **Katzmarzyk PT, Church TS, Blair SN.** Cardiorespiratory fitness attenuates the effects of the metabolic syndrome on all-cause and cardiovascular disease mortality in men. *Arch Intern Med* 164: 1092–1097, 2004.
21. **Kuan JW, Kuan SS, Guilbault GG.** Determination of plasma glucose with use of a stirrer containing immobilized glucose dehydrogenase. *Clin Chem* 23: 1058–1061, 1977.
22. **Lagou V, Scott RA, Manios Y, Chen TL, Wang G, Grammatikaki E, Kortsalioudaki C, Liarigkovinos T, Moschonis G, Roma-Giannikou E, Pitsiladis YP.** Impact of peroxisome proliferator-activated receptors gamma and delta on adiposity in toddlers and preschoolers in the GENESIS Study. *Obesity (Silver Spring)* 16: 913–918, 2008.
23. **Lakka TA, Laaksonen DE, Lakka HM, Mannikko N, Niskanen LK, Rauramaa R, Salonen JT.** Sedentary lifestyle, poor cardiorespiratory fitness, and the metabolic syndrome. *Med Sci Sports Exerc* 35: 1279–1286, 2003.
24. **LaMonte MJ, Barlow CE, Jurca R, Kampert JB, Church TS, Blair SN.** Cardiorespiratory fitness is inversely associated with the incidence of metabolic syndrome: a prospective study of men and women. *Circulation* 112: 505–512, 2005.
25. **Lee S, Kuk JL, Katzmarzyk PT, Blair SN, Church TS, Ross R.** Cardiorespiratory fitness attenuates metabolic risk independent of abdominal subcutaneous and visceral fat in men. *Diabetes Care* 28: 895–901, 2005.
26. **Masud S, Ye S.** Effect of the peroxisome proliferator activated receptor-gamma gene Pro12Ala variant on body mass index: a meta-analysis. *J Med Genet* 40: 773–780, 2003.
27. **McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G.** Use of metabolic markers to identify overweight individuals who are insulin resistant. *Ann Intern Med* 139: 802–809, 2003.
28. **Meirhaeghe A, Amouyel P.** Impact of genetic variation of PPARgamma in humans. *Mol Genet Metab* 83: 93–102, 2004.
29. **Meirhaeghe A, Fajas L, Helbecque N, Cottel D, Auwerx J, Deeb SS, Amouyel P.** Impact of the peroxisome proliferator activated receptor gamma2 Pro12Ala polymorphism on adiposity, lipids and non-insulin-dependent diabetes mellitus. *Int J Obes Relat Metab Disord* 24: 195–199, 2000.
30. **Meirhaeghe A, Fajas L, Helbecque N, Cottel D, Lebel P, Dallongeville J, Deeb S, Auwerx J, Amouyel P.** A genetic polymorphism of the peroxisome proliferator-activated receptor gamma gene influences plasma leptin levels in obese humans. *Hum Mol Genet* 7: 435–440, 1998.
31. **Miyachi M, Tanaka H, Yamamoto K, Yoshioka A, Takahashi K, Onodera S.** Effects of one-legged endurance training on femoral arterial and venous size in healthy humans. *J Appl Physiol* 90: 2439–2444, 2001.
32. **Miyatani M, Kawano H, Masani K, Gando Y, Yamamoto K, Tanimoto M, Oh T, Usui C, Sanada K, Higuchi M, Tabata I, Miyachi M.** Required muscle mass for preventing lifestyle-related diseases in Japanese women. *BMC Public Health* 8: 291, 2008.
33. **Mori H, Ikegami H, Kawaguchi Y, Seino S, Yokoi N, Takeda J, Inoue I, Seino Y, Yasuda K, Hanafusa T, Yamagata K, Awata T, Kadowaki T, Hara K, Yamada N, Gotoda T, Iwasaki N, Iwamoto Y, Sanke T, Nanjo K, Oka Y, Matsutani A, Maeda E, Kasuga M.** The Pro12 –>Ala substitution in PPAR-gamma is associated with resistance to development of diabetes in the general population: possible involvement in impairment of insulin secretion in individuals with type 2 diabetes. *Diabetes* 50: 891–894, 2001.
34. **Mori Y, Kim-Motoyama H, Katakura T, Yasuda K, Kadowaki H, Beamer BA, Shuldiner AR, Akanuma Y, Yazaki Y, Kadowaki T.** Effect of the Pro12Ala variant of the human peroxisome proliferator-activated receptor gamma 2 gene on adiposity, fat distribution, and insulin

sensitivity in Japanese men. *Biochem Biophys Res Commun* 251: 195–198, 1998.

35. **Morini E, Tassi V, Capponi D, Ludovico O, Dallapiccola B, Trischitta V, Prudente S.** Interaction between PPARgamma2 variants and gender on the modulation of body weight. *Obesity (Silver Spring)* 16: 1467–1470, 2008.
36. **Nelson TL, Fingerlin TE, Moss LK, Barmada MM, Ferrell RE, Norris JM.** Association of the peroxisome proliferator-activated receptor gamma gene with type 2 diabetes mellitus varies by physical activity among non-Hispanic whites from Colorado. *Metabolism* 56: 388–393, 2007.
37. **Okuno A, Tamemoto H, Tobe K, Ueki K, Mori Y, Iwamoto K, Umesono K, Akanuma Y, Fujiwara T, Horikoshi H, Yazaki Y, Kadowaki T.** Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. *J Clin Invest* 101: 1354–1361, 1998.
38. **Orakzai RH, Orakzai SH, Nasir K, Roguin A, Pimentel I, Carvalho JA, Meneghello R, Blumenthal RS, Santos RD.** Association of increased cardiorespiratory fitness with low risk for clustering of metabolic syndrome components in asymptomatic men. *Arch Med Res* 37: 522–528, 2006.
39. **Paffenbarger RS Jr, Blair SN, Lee IM, Hyde RT.** Measurement of physical activity to assess health effects in free-living populations. *Med Sci Sports Exerc* 25: 60–70, 1993.
40. **Pihlajamaki J, Miettinen R, Valve R, Karjalainen L, Mykkanen L, Kuusisto J, Deeb S, Auwerx J, Laakso M.** The Pro12A1a substitution in the peroxisome proliferator activated receptor gamma 2 is associated with an insulin-sensitive phenotype in families with familial combined hyperlipidemia and in nondiabetic elderly subjects with dyslipidemia. *Atherosclerosis* 151: 567–574, 2000.
41. **Rankinen T, Zuberi A, Chagnon YC, Weisnagel SJ, Argyropoulos G, Walts B, Perusse L, Bouchard C.** The human obesity gene map: the 2005 update. *Obesity (Silver Spring)* 14: 529–644, 2006.
42. **Ringel J, Engeli S, Distler A, Sharma AM.** Pro12Ala missense mutation of the peroxisome proliferator activated receptor gamma and diabetes mellitus. *Biochem Biophys Res Commun* 254: 450–453, 1999.
43. **Satoh H, Kishi R, Tsutsui H.** Body mass index can similarly predict the presence of multiple cardiovascular risk factors in middle-aged Japanese subjects as waist circumference. *Intern Med* 49: 977–982, 2010.
44. **Tai ES, Corella D, Deurenberg-Yap M, Adiconis X, Chew SK, Tan CE, Ordovas JM.** Differential effects of the C1431T and Pro12Ala PPARgamma gene variants on plasma lipids and diabetes risk in an Asian population. *J Lipid Res* 45: 674–685, 2004.
45. **Takata N, Awata T, Inukai K, Watanabe M, Ohkubo T, Kurihara S, Inaba M, Katayama S.** Pro12Ala substitution in peroxisome proliferator-activated receptor gamma 2 is associated with low adiponectin concentrations in young Japanese men. *Metabolism* 53: 1548–1551, 2004.
46. **Tontonoz P, Hu E, Spiegelman BM.** Regulation of adipocyte gene expression and differentiation by peroxisome proliferator activated receptor gamma. *Curr Opin Genet Dev* 5: 571–576, 1995.
47. **Valve R, Sivenius K, Miettinen R, Pihlajamaki J, Rissanen A, Deeb SS, Auwerx J, Uusitupa M, Laakso M.** Two polymorphisms in the peroxisome proliferator-activated receptor-gamma gene are associated with severe overweight among obese women. *J Clin Endocrinol Metab* 84: 3708–3712, 1999.
48. **Vigouroux C, Fajas L, Khallouf E, Meier M, Gyapay G, Lascols O, Auwerx J, Weissenbach J, Capeau J, Magre J.** Human peroxisome proliferator-activated receptor-gamma2: genetic mapping, identification of a variant in the coding sequence, and exclusion as the gene responsible for lipoatrophic diabetes. *Diabetes* 47: 490–492, 1998.
49. **Weiss EP, Kulaputana O, Ghiu IA, Brandauer J, Wohn CR, Phares DA, Shuldiner AR, Hagberg JM.** Endurance training-induced changes in the insulin response to oral glucose are associated with the peroxisome proliferator-activated receptor-gamma2 Pro12Ala genotype in men but not in women. *Metabolism* 54: 97–102, 2005.
50. **Whaley MH, Kampert JB, Kohl HW, 3rd, Blair SN.** Physical fitness and clustering of risk factors associated with the metabolic syndrome. *Med Sci Sports Exerc* 31: 287–293, 1999.
51. **Willson TM, Cobb JE, Cowan DJ, Wiethe RW, Correa ID, Prakash SR, Beck KD, Moore LB, Kliewer SA, Lehmann JM.** The structure-activity relationship between peroxisome proliferator-activated receptor gamma agonism and the antihyperglycemic activity of thiazolidinediones. *J Med Chem* 39: 665–668, 1996.
52. **Yamauchi T, Kamon J, Waki H, Murakami K, Motojima K, Komeda K, Ide T, Kubota N, Terauchi Y, Tobe K, Miki H, Tsuchida A, Akanuma Y, Nagai R, Kimura S, Kadowaki T.** The mechanisms by which both heterozygous peroxisome proliferator-activated receptor gamma (PPARgamma) deficiency and PPARgamma agonist improve insulin resistance. *J Biol Chem* 276: 41245–41254, 2001.
53. **Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T.** The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med* 7: 941–946, 2001.
54. **Yen CJ, Beamer BA, Negri C, Silver K, Brown KA, Yarnall DP, Burns DK, Roth J, Shuldiner AR.** Molecular scanning of the human peroxisome proliferator activated receptor gamma (hPPAR gamma) gene in diabetic Caucasians: identification of a Pro12Ala PPAR gamma 2 missense mutation. *Biochem Biophys Res Commun* 241: 270–274, 1997.

特定健診・保健指導の標準的な質問票を用いた身体活動評価の妥当性

川上 諒子(カワカミ リョウコ)*　宮地 元彦(ミヤチ モトヒコ)*

目的　本研究は，「標準的な健診・保健指導プログラム（確定版）」の標準的な質問票を用いた身体活動調査と3次元加速度計を用いて測定した歩数や身体活動量との比較を行うとともに，全身持久力との関係についても比較検討することを目的とした。

方法　被験者は，20から69歳までの成人男女483人であった。「標準的な健診・保健指導プログラム（確定版）」の標準的な質問票より，運動習慣，身体活動，歩行速度に関する3つの質問を用いた。質問は「はい」または「いいえ」で回答する形式であった。3つの質問に「はい」と回答した個数をもとに4つの活動レベルに分類した。歩数および身体活動量の測定には，3次元加速度計が用いられ，1日あたりの平均歩数，3メッツ未満，3メッツ以上，4メッツ以上の活動強度の身体活動量（メッツ・時）が測定された。さらに，運動負荷試験により最高酸素摂取量が測定され，全身持久力の指標とした。

結果　運動習慣，身体活動，歩行速度のいずれの質問においても，「はい」と答えた者は「いいえ」と答えた者より1日あたりの歩数，3メッツ以上および4メッツ以上の身体活動量ならびに全身持久力が有意に高いことが示された。「健康づくりのための運動基準2006」で示された身体活動量の基準において各質問による感度は62～73%，特異度は45～71%であった。また，活動レベル2をカットオフ値とした際に感度と特異度の和が最高となり，感度73%，特異度68%であった。全身持久力の基準における感度や特異度は，身体活動量の基準によるものよりもやや低かった。

結論　特定健診・保健指導の標準的な質問票を用いた身体活動調査によって，精度としてはそれほど高くないものの，簡易的な質問に回答するだけで日常の身体活動状況をある程度推定することが可能であることが示唆された。

Key words：質問紙，運動，身体活動，全身持久力，特定健診・保健指導，健康づくりのための運動基準2006

I　緒　　言

身体活動量や全身持久力が高い者は生活習慣病の発症リスクが低いことが報告されている[1~4]。わが国では，平成18年に健康づくりのための身体活動量や全身持久力の基準値を定めた「健康づくりのための運動基準2006」および「健康づくりのための運動指針2006」が策定された[5,6]。また，平成20年4月からは，生活習慣病予防のために医療保険者に対して特定健康診査・特定保健指導の実施が定められた。そのため，近年では保健指導をはじめとする様々な場において対象者の身体活動量や全身持久力をより簡便に評価できる方法が必要とされている。

身体活動量の評価法には，二重標識水法，心拍数法，加速度計法，歩数計法，生活活動記録法，質問紙法など様々な方法がある[7]。中でも，質問紙法は他の評価法と比較して短時間で安価に行うことができ，誰もが容易に調査を行うことができるという利点を持つ。さらに，一度に多くの人を対象とした調査も可能であることから，疫学調査や保健指導の現場などでの活用が可能である。しかしながら，質問紙法には回答者の主観やあいまいな記憶などによるバイアスが入りやすく，客観性や正確性に乏しいという欠点もみられる。

平成19年に厚生労働省より「標準的な健診・保健指導プログラム（確定版）」が発表され[8]，平成20年からは特定健診・保健指導で活用されている。このプログラムには，対象者のリスクや生活習慣状況を把握するための「標準的な質問票」が示されてお

* 独立行政法人国立健康・栄養研究所健康増進プログラム
連絡先：〒162-8636 東京都新宿区戸山1-23-1
独立行政法人国立健康・栄養研究所健康増進プログラム　宮地元彦

り，身体活動に関する質問も3問含まれている。質問内容は，「健康づくりのための運動基準2006」で定められた，週4メッツ・時の余暇時間における運動量，週23メッツ・時の身体活動量の基準が達成されているか否かを意図したものに加え，欧米の疫学研究で生活習慣病発症リスクとの関連が報告された日常の歩行速度に関する質問が活動強度や全身持久力の評価として含まれたものである[9~11]。しかしながら，この標準的な質問票を用いた身体活動の調査と実際の身体活動量や全身持久力とを比較した，日本人を対象とした報告はない。

そこで本研究では，標準的な質問票を用いた身体活動調査と3次元加速度計を用いて測定した歩数や身体活動量との比較を行うとともに，全身持久力との関係について比較検討を行うことを目的とした。

II　研究方法

1.　被験者

被験者は，20から69歳までの成人男女483名（男性178名，女性305名）であった。本研究を始めるにあたり，独立行政法人国立健康・栄養研究所における研究倫理審査委員会の承認を受けた。また，研究参加者には，本研究の目的や意義，危険性について事前に詳細な説明を行い，研究内容を十分に理解した上で研究参加への同意を得た。被験者の特性を表1に示す。

2.　測定項目および方法

1)　質問票による身体活動調査およびその分類

平成19年に厚生労働省より発表された「標準的な健診・保健指導プログラム（確定版）」の標準的な質問票より，身体活動に関する質問を用いた。回答形式は「はい」または「いいえ」で回答する2件法であり，自記式法とした。質問内容は，「1回30分以上の軽く汗をかく運動を週2日以上，1年以上実施」（以下　運動習慣に関する質問），「日常生活において歩行又は同等の身体活動を1日1時間以上実施」（以下　身体活動に関する質問），「ほぼ同じ年齢の同性と比較して歩く速度が速い」（以下　歩行速度に関する質問）の3つとした。

また，運動習慣，身体活動，歩行速度の3つの質問の回答を組み合わせることにより，4つの活動レベルに分類した。3つの質問において「はい」と答えた個数が3つであった者を「活動レベル3」，2つであった者を「活動レベル2」，1つであった者を「活動レベル1」，そしてすべての質問に対して「いいえ」と答えた者を「活動レベル0」とした。

2)　歩数・身体活動量の測定

歩数および身体活動量の測定には，3次元加速度計（Actimarker EW4800：パナソニック電工社製）が用いられ，日常の身体活動が客観的に評価された。被験者は，加速度計を起床時から就寝時までの間，休日を含めて毎日20日間，腰部前方に装着した。1日あたりの平均歩数，および3メッツ未満，3メッツ以上，4メッツ以上の活動強度の身体活動量（メッツ・時）が測定された。

加速度計の大きさは60×35×13 mm，重さは24 g（電池込み）であった。加速度計には3軸方向（x：上下，y：左右，z：前後）の加速度センサーが内蔵されていた。1分毎の加速度値（Km）は，3軸の合成加速度の標準偏差として以下の式で算出された。

$$\mathrm{Km}=\sqrt{\frac{1}{n-1}\left[\left(\sum_{k=1}^{n}x_k^2+\sum_{k=1}^{n}y_k^2+\sum_{k=1}^{n}z_k^2\right)-\frac{1}{n}\left\{\left(\sum_{k=1}^{n}x_k\right)^2+\left(\sum_{k=1}^{n}y_k\right)^2+\left(\sum_{k=1}^{n}z_k\right)^2\right\}\right]}$$

x_k, y_k, z_kは1分毎における各軸方向の加速度を示しており，nは1分間にサンプリングされる個数である。加速度のサンプリング周波数は20 Hzであり，算出された加速度値は内蔵されたアルゴリズムによってメッツに変換され，1分毎に平均した値が時刻暦とともに内蔵メモリに蓄積された。この3次元加速度計の妥当性を検討した先行研究において，7種類の家事作業と7水準の歩行，走行速度における酸素摂取量との間に高い相関（r＝0.93）が認められている[12]。また，二重標識水法によって測定された総消費エネルギー量との間にも高い相関（r＝0.84）が認められており，1次元の加速度計よりも精度が高いことが報告されている[13]。

「健康づくりのための運動基準2006」で示された身体活動量の基準値「3メッツ以上の活動強度の身

表1　被験者特性

	男　性	女　性	全　体
N	178	305	483
年齢（歳）	44±10	50±9	48±10
身長（cm）	170.3±5.5	157.0±5.5	161.9±8.5
体重（kg）	68.5±8.5	55.1±8.4	60.1±10.6
BMI（kg/m^2）	23.6±2.6	22.4±3.3	22.8±3.1
歩数（歩/日）	1,0643±3,668	11,093±3,929	10,927±3,838
3メッツ未満の身体活動量（メッツ・時/日）	14.5±3.1	17.7±3.2	16.5±3.6
3メッツ以上の身体活動量（メッツ・時/日）	3.7±2.3	4.0±2.3	3.9±2.3
4メッツ以上の身体活動量（メッツ・時/日）	1.5±1.6	1.4±1.6	1.4±1.6
最高酸素摂取量（ml/kg/min）	35.6±7.8	29.4±6.2	31.7±7.5

平均値±標準偏差。

体活動を23メッツ・時/週」に相当する，1日あたり3.3メッツ・時を満たした者を身体活動量の基準達成者とした。

3)　全身持久力の測定

全身持久力は，自転車エルゴメーター（Ergomedic 828E: Monark社製）を用いた漸増負荷法により測定された。45～90 Wで5分間のウォーミングアップを行わせた後，その強度から1分毎に15 Wずつ負荷を増加させ，疲労困憊まで至らしめた。なお，ペダルの回転数は毎分60回転とした。自覚的運動強度（RPE）が17を越えた頃を目安とし，運動終了前の2～3分間程度，疲労困憊に至るまで30秒毎に運動中の呼気ガスを採取した。呼気ガスの分析には，自動質量分析機（ARCO-1000：アルコシステム社製）が用いられ，酸素および二酸化炭素の濃度が測定された。さらに，乾式ガスメータ（DC-5：品川社製）を用いて換気量が測定され，酸素摂取量が算出された。測定により得られた酸素摂取量の最高値を最高酸素摂取量とし，全身持久力の指標とした。運動中は，ハートモニター（Life Scope 6：日本光電社製）により，心電図および心拍数が連続的にモニタリングされた。

「健康づくりのための運動基準2006」で示された性・年代別の全身持久力（最大酸素摂取量）の基準値を表2に示した。この基準値を満たした者を全身持久力の基準達成者とした。

3.　統計処理

測定値は，平均値±標準偏差，または95%信頼区間で示した。各質問の回答および3つの質問の組合せによる活動レベル間の連続変数（歩数・身体活動量・全身持久力など）の平均値や分布の比較には一元配置分散分析を用いた。なお，各質問や活動レベルにおいて年齢や性別で有意差が認められた場合には，有意差が認められた因子をそれぞれ共変量とした共分散分析を用い解析をした。多重比較検定にはStudent Newman-Keuls法を用いた。また，各質問の回答および3つの質問の組合せによる活動レベル間のカテゴリー変数（「健康づくりのための運動基準2006」で示された身体活動量および全身持久力の基準達成者の割合など）の頻度の比較にはχ^2検定を用いた。統計的有意水準はすべて5%未満とした。

各質問の回答および3つの質問を組合せた活動レベルによる身体活動量と全身持久力の評価の妥当性を検証するために，各質問と活動レベルごとに，感度，特異度，陽性反応適中度，陰性反応適中度を算出した。

表2　健康づくりのための全身持久力（最大酸素摂取量）の基準値（ml/kg/min）

	20歳代	30歳代	40歳代	50歳代	60歳代
男性	40	38	37	34	33
女性	33	32	31	29	28

「健康づくりのための運動基準2006」。

Ⅲ　研究結果

1.　各質問の回答による比較

各質問の回答結果における歩数，身体活動量を表3に示した。1日あたりの平均歩数，3メッツ以上および4メッツ以上の身体活動量に関して，運動習慣，身体活動，歩行速度のいずれの質問においても「はい」と答えた者は「いいえ」と答えた者よりそれぞれ統計上有意に高い値が認められた。3メッツ未満の身体活動量においては，3つのいずれの質問に対する回答結果においても有意な差が認められなかった。

全身持久力は，運動習慣，身体活動，歩行速度のいずれの質問においても「はい」と答えた者は「いいえ」と答えた者と比較してそれぞれ統計上有意に高い値が認められた（表3）。

2.　3つの質問の組み合わせによる比較

3つの質問を組み合わせることで得られた活動レベルと歩数，身体活動量の関連を表4に示した。歩数および4メッツ以上の身体活動量は，活動レベル0, 1の者と比較して，2および3の者で統計上有意に高い値が認められた。3メッツ以上の身体活動量は，すべての活動レベル間で有意な差が認められ，活動レベルが高い者ほど統計上有意に高い値となった。3メッツ未満の身体活動量においては，活動レベル間で有意な差がなかった。

3つの質問の活動レベルにおける全身持久力を表4に示した。活動レベル2および3の者は，活動レベル0, 1の者と比較して全身持久力が統計上有意に高かった。さらに，活動レベル3の者は，活動レベル2の者よりも有意に高い値が認められた。

3.　質問の回答と「健康づくりのための運動基準2006」

各質問の回答結果と「健康づくりのための運動基準2006」で示された身体活動量および全身持久力の基準達成状況を表5に示した。身体活動量の基準達成者のうち「はい」と答えた者は，いずれの質問においても「いいえ」と答えた者より統計上有意に多かった。全身持久力の基準では，運動習慣と身体活動の質問において基準達成者で「はい」と回答した者が「いいえ」と回答した者より有意に多かった。

3つの質問の活動レベルにおける基準達成状況を