Table 4 Association of groups divided by the WOMAC function score with the occurrence of certified need of care in the LTCI system

	Overall population		Men		Women	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
WF ≥ 4 pts vs WF < 4 pts	2.54 (1.76, 3.67)	<0.001	1.85 (1.01, 3.39)	0.045	3.13 (1.95, 5.02)	<0.001
WF ≥ 5 pts vs WF < 5 pts	2.35 (1.64, 3.36)	<0.001	1.88 (1.03, 3.43)	0.040	2.71 (1.73, 4.27)	<0.001
WF ≥ 6 pts vs WF < 6 pts	2.50 (1.75, 3.58)	<0.001	1.84 (1.00, 3.39)	0.051	3.03 (1.93, 4.76)	<0.001

Hazard ratios (HRs) and 95 % confidence intervals (CIs) were determined by Cox proportional hazards regression analysis after adjusting for age, sex, body mass index, and region in the overall population, and after adjusting for age, body mass index, and region in men and in women, respectively

WOMAC the Western Ontario and McMaster Universities Arthritis Index, *LTCI* long-term care insurance system, *WF* WOMAC function score

Table 5 Association of the WOMAC function score with the occurrence of different certified need of care levels in the LTCI system

Outcome variable	Overall population		Men		Women	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
RSL1–2 and RCL 1–5	1.05 (1.03, 1.06)	<0.001	1.03 (1.01, 1.06)	0.008	1.05 (1.04, 1.07)	<0.001
RCL 1–5	1.05 (1.03, 1.07)	<0.001	1.04 (1.00, 1.07)	0.046	1.06 (1.03, 1.08)	<0.001
RCL 2–5	1.06 (1.04, 1.08)	<0.001	1.04 (1.01, 1.08)	0.015	1.06 (1.04, 1.09)	<0.001
RCL 3–5	1.05 (1.03, 1.08)	<0.001	1.05 (0.99, 1.10)	0.099	1.06 (1.02, 1.09)	0.001
RCL 4–5	1.04 (1.00, 1.08)	0.048	1.02 (0.95, 1.10)	0.501	1.05 (1.00, 1.10)	0.057
RCL 5	1.01 (0.93, 1.09)	0.830	0.99 (0.82, 1.20)	0.945	1.01 (0.93, 1.11)	0.780

Hazard ratios (HRs) and 95 % confidence intervals (CIs) were determined by Cox proportional hazards regression analysis after adjusting for age, sex, body mass index, and region in the overall population, and after adjusting for age, body mass index, and region in men and in women, respectively

WOMAC the Western Ontario and McMaster Universities Arthritis Index, *LTCI* long-term care insurance system, *RSL* requiring support level, *RCL* requiring long-term care level

associated with the occurrence of certified need of care compared with the group with a score of <5 with the highest HR [HR 1.88, 95 % CI (1.03–3.43)].

Furthermore, we examined association of the WOMAC function domain with the occurrence of different certified need of care levels in the LTCI system (Table 5). When the outcome variable of the occurrence was defined as requiring support level (RSL) 1–2 and requiring long-term care level (RCL) 1–5, RCL 1–5, and RCL 2–5, there were significant associations in the overall population, in men, and in women, respectively. When the outcome variable of the occurrence was defined as RCL 3–5, there were significant associations in the overall population and in women. When the outcome variable of the occurrence was defined as RCL 4–5, there was significant association in the overall population.

Discussion

The present study determined association of physical ADLs with the incidence of certified need of care in the national LTCI system in elderly participants of Japanese population-based cohorts. All 17 items in the WOMAC function domain were significantly associated with the occurrence of certified need of care in the overall population. ROC curve analysis showed that cut-off values of the WOMAC function score of around 4–6 maximized the sum of sensitivity and specificity of the occurrence of certified need of care. Furthermore, multivariate Cox hazards regression analysis revealed that the group with WOMAC function score ≥4 was significantly associated with the occurrence of certified need of care with the highest HR after adjusting for confounders in the overall population and in women, while the group with WOMAC function score ≥5 was significantly associated with the highest HR in men.

In the present study, we could not obtain information on causes of certified need of care in the LTCI system. Therefore, we could not analyze the direct association of each causing condition with the WOMAC function domain. The Government of Japan reported that the top five leading causes of certified need of care were cerebral stroke (21.5 %), dementia (15.3 %), asthenia as a result of older age (13.7 %), joint disease (10.9 %) and fall-related fracture (10.2 %), comprising 71.6 % of all causes in 2010 [10]. Based on these data, most of the causes of incident certification in the present study are inferred to be among the top five leading conditions. Although we could not

know the exact percentage of each causing condition, joint disease and fall-related fracture are inferred to represent approximately 20 % in total causes of incident certification in the present study, and cerebral stroke, dementia, and asthenia as a result of older age are inferred to represent approximately 50 % in total causes of incident certification.

The Government of Japan also reported that the percentage of joint disease and fall-related fracture was 16.7 % for the cause of RCL 1–5 [10]. Furthermore, it was 17.6, 19.8, 14.8, 17.4, and 9.8 % for the cause of RCL 1, 2, 3, 4, and 5, respectively [10]. Although we could not know the exact percentage of joint disease and fall-related fracture for the cause of each RCL in the present study, the percentage for the cause of RCL 1–4 is inferred to be approximately 15 % or more based on the data of the Government of Japan, which may be the reason why the WOMAC domain was significantly associated with the occurrence of certified need of care including RCLs 1–4 in the overall population.

The WOMAC physical function domain assesses difficulties in ADLs, including going up/down stairs, getting in/out of a car and bath, shopping, and household duties. Therefore, results of the present study indicate that the severity of physical dysfunction in ADLs predicts subsequent deterioration in ADLs, leading to the occurrence of certified need of care. Previous studies reported that low physical function was a predictor of subsequent ADL disability in the elderly [11, 12]. Although no previous studies have investigated the association of physical ADLs with the incidence of certified need of care in the national LTCI system in large-scale population-based cohorts, those previous findings are consistent with the present results in that low physical activity predicted subsequent deterioration in ADLs.

All 17 items in the WOMAC domain were significantly associated with the occurrence of certified need of care in women. On the other hand, 9 of 17 items were significantly associated with the occurrence of certified need of care in men. In addition, the HR for each item in the association was higher in women than in men for 15 of 17 items. The sex difference identified in this association may be due to the difference in the prevalence of knee osteoarthritis between the sexes. Muraki et al. [13] reported that prevalence of radiographic knee osteoarthritis determined by the Kellgren–Lawrence grade ≥ 2 was 47.0 % in men and 70.2 % in women, respectively, in subjects aged 60 years and older in Japanese population-based cohorts. Therefore, women are more likely than men to be affected by knee osteoarthritis and have difficulties in physical function of the lower extremities, leading to higher scores on the WOMAC function scale. Another reason for the sex differences may be the weaker muscle strength in women; muscle strength in men is higher than that in women in all decades of life [14], which may obscure the association in men, as muscle strength has been reported to be inversely associated with the WOMAC domains [15].

Functional declines in locomotive organs including physical ADLs usually progress slowly and gradually. As such, it may be difficult for people to recognize this decline in their daily life. Therefore, it is of particular importance to raise awareness of the growing risk caused by such disorders, and to take action to improve and maintain the health of the locomotive organs. The Japanese Orthopaedic Association proposed the concept of "locomotive syndrome" in 2007 for the promotion of preventive healthcare of the locomotive organs [16–18]. Locomotive syndrome refers to conditions under which the elderly have been receiving support or long-term care, or high-risk conditions under which they may soon require support or long-term care, that are caused by musculoskeletal disorders [16–18]. Population approaches, including promotion of the concept of locomotive syndrome to both younger and older generations, are important, in addition to high-risk approaches, including identifying those at risk for certified need of care and practicing intervention programs to reduce the risk of certified need of care.

Because the WOMAC function scale is a self-assessment questionnaire that is easy to conduct and evaluate, it can be used to screen elderly persons at high risk of certified need of care in the LTCI system. Multivariate Cox hazards regression analysis showed that a WOMAC function score of 5 in men and 4 in women best discriminated between the occurrence and the non-occurrence group of certified need of care in this study population. Elderly men with a WOMAC function score ≥ 5 had a 1.88-fold higher risk of occurrence of certified need of care compared with elderly men with a score <5. Elderly women with a WOMAC function score ≥ 4 had a 3.13-fold higher risk of occurrence of certified need of care compared with elderly women with a score <4. Elderly persons screened by these cut-off values should receive early intervention for the prevention of subsequent deterioration in ADLs that could lead to certified need of care. Further studies, along with the accumulation of epidemiologic evidence, are necessary to develop intervention programs that are safe and effective for elderly subjects who are at high risk of certified need of care.

There are some limitations in the present study. First, we could not obtain information on causes of certified need of care in the LTCI system. Therefore, we could not analyze the direct association of each causing condition with measured factors, and could not determine the risk factors for occurrence of certified need of care with respect to each causing condition. The Japanese government reported that the top five leading causes of certified need of care were cerebral stroke, dementia, asthenia, osteoarthritis, and fall-related fracture, comprising 71.6 % of all causes in 2010 [10]. Based on these data, most of the causes of incident certification in the present

study are inferred to be among the top five leading conditions. Additional studies are necessary to identify those direct associations. Second, participants at baseline in the present study were those who could walk to the survey site and could understand and sign an informed consent form. Since those who could not were not included in the analyses, the study participants do not truly represent the general population due to health bias, which should be taken into consideration when generalizing the results of the present study.

In conclusion, the present study determined association of physical ADLs with the occurrence of certified need of care in the LTCI system in elderly participants of Japanese population-based cohorts. The severity of physical dysfunction is a predictor of the occurrence of certified need of care. Further studies are necessary to develop intervention programs that are safe and effective for elderly individuals who are at high risk of certified need of care.

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Conflict of interest There are no conflicts of interest.

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Original Article

Relationship Between Physical Activity and Chronic Musculoskeletal Pain Among Community-Dwelling Japanese Adults

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ABSTRACT

Background: Both little and excessive physical activity (PA) may relate to chronic musculoskeletal pain. The primary objective of this study was to characterize the relationship of PA levels with chronic low back pain (CLBP) and chronic knee pain (CKP).

Methods: We evaluated 4559 adults aged 40–79 years in a community-based cross-sectional survey conducted in 2009 in Shimane, Japan. We used self-administered questionnaires to assess sociodemographics and health status: PA was assessed by the International Physical Activity Questionnaire, and CLBP and CKP were assessed by a modified version of the Knee Pain Screening Tool. We examined relationships of PA with prevalence of CLBP and CKP using Poisson regression, controlling for potential confounders.

Results: CLBP and CKP were both prevalent (14.1% and 10.7%, respectively) and associated with history of injury, medication use, and consultation with physicians. PA was not significantly related to CLBP or CKP ($P > 0.05$) before or after adjustment for potential confounders. For example, compared with adults reporting moderate PA (8.25–23.0 MET-hours/week), prevalence ratios for CKP adjusted for sex, age, education years, self-rated health, depressive symptom, smoking, chronic disease history, and body-mass index were 1.12 (95% confidential interval [CI] 0.84–1.50) among those with the lowest PA and 1.26 (95% CI 0.93–1.70) among those with the highest PA (P quadratic = 0.08). The prevalence ratios were further attenuated toward the null after additional adjustment for history of injury, medication use, and consultation (P quadratic = 0.17).

Conclusions: This cross-sectional study showed that there were no significant linear or quadratic relationships of self-reported PA with CLBP and CKP. Future longitudinal study with objective measurements is needed.

Key words: exercise; musculoskeletal pain; arthritis; epidemiology; public health

INTRODUCTION

Musculoskeletal disorders are a major burden on individuals, health systems, and society, contributing meaningfully to indirect costs[1] and disability worldwide.[2] Further, chronic musculoskeletal pain (CMP), a major symptom of musculoskeletal disorders,[3–6] worsens quality of life and physical functioning later in life.[7,8] In the United States, 28.8% of men and 26.6% of women reported feeling some pain.[9] The lifetime risk of low back pain in Japan is estimated to be 83%.[10] However, despite its importance to public health, evidence linking lifestyle to CMP remains to be established.

Physical activity (PA), including exercise therapy, is recommended as a non-pharmacological intervention for

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CMP.[11,12] Pharmacological treatments, including nonsteroidal anti-inflammatory drugs, are also commonly prescribed. Considering the expense of prescriptions and side effects of such treatments,[13] increasing PA should receive greater priority both as a therapeutic agent and as preventative action against CMP. However, the relationship between PA levels and CMP has not been established yet.

Recently, both too little PA and too much PA were found to be hazardous to spinal health,[14,15] indicating a U-shaped relationship between PA and chronic low back pain (CLBP). However, few studies have examined the dose-response relationship between PA and CMP.[15–18]

When examining the relationship between PA and CMP, weight status and musculoskeletal injury need to be accounted for, since adiposity is an established risk factor for knee osteoarthritis and CMP.[19–22] Among overweight individuals, excessive PA may cause high physical load on the knee joint, leading to chronic knee pain (CKP).[23] This mechanism suggests that excess PA may cause CMP, especially among overweight adults. Injury is also an established risk factor for CMP.[23,24] Excess PA increases the probability of experiencing injury,[25,26] and musculoskeletal injury may reduce PA levels,[27,28] potentially leading to weight gain.[29] For these reasons, it is important to consider both weight status and injury history when investigating the association of PA with CMP. To our knowledge, a history of injury has been accounted for only in studies examining the risk of knee osteoarthritis,[23,30,31] while studies of the relationship between PA and CMP in the general population typically have not taken injury history into account. In addition, adults who have history of injury are likely to take medications and consult physicians, and these pain management factors may also affect pain itself as well as daily habits (such as PA). Thus, consideration of these factors is also important.

To fill the gap in knowledge on the potential role of PA in the development of CMP, we examined cross-sectional associations of PA with CLBP and CKP among adults in a community-based survey in Japan, taking into account potential confounding by body weight, history of joint injuries, and pain management factors. We also examined *post hoc* how these factors could influence associations between common demographic variables with CLBP and CKP.

METHODS

Data collection

We cross-sectionally evaluated observations from an ongoing community-based intervention study for community-level improvement in levels of PA.[32] In October 2009, invitation letters, consent forms, and questionnaires were mailed to 6000 residents randomly selected from the city registry in Unnan City (population 43 520, area 553.4 km^2), a rural mountainous region in Shimane, Japan. Men and women aged 40 to 79 years were invited to participate; excluded were those in assisted living facilities, those who required long-term care, and those who could not complete the questionnaires by themselves. We took a pragmatic approach to increase our survey response rate, including the use of personalised and relatively short questionnaires[33] and sending postcard reminders to non-responders.

A total of 4559 adults (76.0%) responded to the initial survey of the trial and were considered eligible for the present study. Written informed consent was obtained from each participant. This study was approved by the research ethics committee of the Physical Education and Medicine Research Center UNNAN (H21-10-13-1).

Measures

Sex and age were derived from the city registry, and other sociodemographic variables were obtained from self-administered questionnaires. We inquired about weight and height (used for calculating body mass index [BMI] in kg/m^2), years of education, self-rated health (very good, good, poor, or very poor),[34] depressive symptom (yes or no),[35] smoking (never, past, or current), and chronic disease history (hypertension, hyperlipidaemia, diabetes, hyperuricaemia, stroke, heart disease, kidney and urologic diseases, liver disease, gastrointestinal disease, endocrine disease, or cancer). These covariates were selected because they previously have been reported to be associated with PA, musculoskeletal morbidity, or both.[23,36]

Musculoskeletal pain

CLBP and CKP were assessed using a questionnaire (available as web-only supplemental material eQuestionnaire 1) that has questions similar to those in the Knee Pain Screening Tool (KNEST), except for questions about use of health services (which were not examined in this study).[37,38] The KNEST was previously developed to screen and identify individuals who have knee pain in a general population. CLBP and CKP were defined as current pain (ie, episodes of pain at the time of the questionnaire) that had lasted longer than 3 months in the past year.[39] We assessed the test-retest reliability of CLBP and CKP in study subjects by mailing the questionnaire twice to 500 randomly-selected adults aged 40–84 years, separated by an interval of 10 days. These were individuals living in Unnan who were not invited to participate in the main trial/survey. Evaluating the 206 respondents (response rate 41.2%; mean and standard deviation [SD] of age 63.4 and 11.9 years; 51.4% women) to both questionnaires, we observed moderate reliability (Cohen's kappa 0.49 for CLBP and 0.72 for CKP).

We also obtained information on a visual analogue scale (VAS) for intensity of pain. We defined "severe chronic pain" as chronic pain with a VAS pain score ≥75 on a 100-point scale.[40] However, the prevalence of severe chronic pain was

low (low back: $n = 96$, 2.4%; knee: $n = 83$, 2.0%) in this general population. Thus, we were unable to analyze this outcome in detail in the current study. We also asked about a history of low back injury and knee injury, medication use, and consultation with physicians for low back or knee pain. These factors were included in analyses as dichotomous variables (yes or no for each item).

Physical activity

We used the Japanese short version of the International Physical Activity Questionnaire (IPAQ),[41] for which external reliability and validity have been reported elsewhere.[42,43] The IPAQ asks separate questions about time spent on walking, moderate physical activity (MPA), and vigorous physical activity (VPA) in a typical week.

We estimated total weekly PA by multiplying the reported duration (hours) per week of walking, MPA, and VPA by their Metabolic Equivalent of Tasks (METs; walking = 3.3 METs; MPA = 4.0 METs; and VPA = 8.0 METs) to obtain estimated energy expenditure in MET-hours per week.[41] Using these values, total moderate-to-vigorous physical activity (MVPA) was defined as 7 days × (3.3 METs × walking hours/day + 4.0 METs × MPA hours/day + 8.0 METs × VPA hours/day). The internal reliability over 10 days of the IPAQ was tested within our study, and found to be acceptable (Spearman correlation $r = 0.64$ among adults aged 40–84 years in the forementioned reliability study). In a validation study conducted among a sample of 95 subjects (40 men and 55 women) aged 62 to 85 (mean [SD], 74.9 [4.5]) years living in Unnan, we compared energy expenditure derived from the IPAQ with that objectively measured by a uniaxial accelerometer (Lifecorder, Suzuken Co., Ltd., Nagoya, Japan[44,45]). The validity ($r = 0.33$) was comparable to that observed in other studies.[42,43]

Statistical analyses

We compared the prevalence of CLBP and CKP in adults with different PA levels, estimating prevalence ratios (PR) by multivariable-adjusted Poisson regression.[46] Poisson regression was used because the prevalence of CLBP and CKP was relatively high (>10% each). We examined CLBP and CKP separately as well as simultaneously using generalized estimating equations because these outcomes were correlated (kappa = 0.20).[47]

We evaluated total MVPA levels both continuously and categorically. To define categories, we chose an MVPA cutpoint of 8.25, corresponding to the WHO recommendation of 2.5 hours/week of MVPA (brisk walking in this case).[48] For those with ≥8.25 MET-hours/week, we used tertiles within this sufficiently active group to determine further cutpoints (23.1, 75.4). Thus, the participants were divided into five categories: 0, 0.01–8.24, 8.25–23.00, 23.01–75.39, and ≥75.40 MET-hours/week. The adjusted PR and 95% confidence intervals (CIs) were then estimated using the middle category (8.25–23.0 MET-hours/week) as the reference category to assess potential non-linear relationships between MVPA and CMP.

When we evaluated MVPA as a continuous variable, we truncated the variable at the 95th percentile value (180 MET-hours/week) and log-transformed the variable to minimize effects of outliers and right-skewed distribution; analyses without truncation and log-transformation produced similar results, although whether the homoscedasticity assumption was met was uncertain (data not shown). In the regression analyses, we separately tested linear and quadratic relationships between MVPA and CMP.

We adjusted for the following potential confounders: sex, age, years of education, self-rated health, depressive symptoms, smoking habit, and chronic disease history (Model 1). In a separate model, we further adjusted for BMI (Model 2), past history of joint injuries (Model 3), and medication use and consultation with physicians (Model 4). Prevalence ratios by each covariate were additionally evaluated. We also assessed whether excess PA was associated with CKP, especially among adults with greater weight, by testing for an interaction between MVPA and BMI for CKP prevalence, and by examining joint categories of BMI (<20, 20–24.9, and ≥25 kg/m^2) and MVPA (<8.25, 8.25–39.59, and ≥39.6 MET-hours/week). For these analyses, we used the median value of MVPA in adults with sufficient PA (39.5 MET-hours/week) for the cutpoint. We further assessed interactions between MVPA and history of injuries (low back or knee) for the combined outcome of either CLBP or CKP. While a prior review recommended exclusion of adults previously experiencing joint injuries in such analyses,[23] our sample size would have been substantially reduced by excluding adults with a history of injury (33% of total). In a sensitivity analyses, we examined only adults without such a history and findings were little changed. Thus, in the present analyses, we included them, treating history of injury as a potential confounder and an effect-modifier.

We examined the associations of the different PA intensities with CLBP and CKP. In these analyses, VPA, MPA, and walking (in minutes per week) were entered into the same model simultaneously. Categorical and continuous analyses were performed separately for each PA intensity.

Missing information was imputed to minimize bias due to missing information and repeated four times, under the assumption that values were missing at random.[49,50] Each imputation was based on regression models including variables used in the main regression analyses. The five imputed datasets were analysed independently and combined for inference, accounting for variability of imputation.[49,50] We also repeated our analyses evaluating adults with complete information only, including 3329 participants. Analyses (two-sided $\alpha < 0.05$) were carried out using SAS version 9.3 (Cary, NC, USA).

Table 1. Characteristics of adults in a community-based survey in Shimane, Japan, 2009 ($n = 4559$)

	Total	Participants who had CLBP	Participants who had CKP
Number of participants	4559	605	471
Physical activity[a]			
MVPA, MET-hours/week	10.6 (0–46.2)	11.6 (0–49.5)	11.6 (0–56.3)
Vigorous physical activity, min/week	0 (0–0)	0 (0–0)	0 (0–10)
Moderate physical activity, min/week	0 (0–40)	0 (0–40)	0 (0–60)
Walking, min/week	120 (0–420)	120 (0–420)	123 (0–510)
Men, %	46.3	49.9	39.5
Age, years	60.9 (10.6)	62.8 (10.6)	65.9 (10.0)
40s, %	17.6	13.2	7.0
50s, %	26.8	24.3	20.4
60s, %	29.8	29.6	28.5
70s, %	25.8	32.9	44.2
Self-rated health			
Excellent or good, %	81.8	61.6	68.9
Education status, years	11.4 (2.4)	11.2 (2.4)	10.8 (2.3)
Chronic disease history, %[b]	62.0	68.4	64.8
Depressive symptom, %	47.6	52.4	72.8
Smoking			
Past smoker, %	8.8	11.4	9.2
Current smoker, %	16.9	18.9	9.6
Body mass index, kg/m^2	22.5 (3.1)	22.7 (3.2)	23.6 (3.1)
Past low back injury, %	23.2	45.1	29.1
Past knee injury, %	16.0	24.1	42.5
Medication use for low back pain, %	18.5	50.2	35.5
Medication use for knee pain, %	11.8	20.6	51.0
Consultation with physicians for low back pain, %	16.3	43.7	26.9
Consultation with physicians for knee pain, %	11.6	17.7	53.0

CLBP, chronic low back pain; CKP, chronic knee pain; MET, metabolic equivalent; MVPA, moderate-to-vigorous physical activity.
Means (standard deviations) for continuous variables and proportions for categorical variables are presented unless stated otherwise.
[a]Median (interquartile range).
[b]Reporting history of any of the following diseases: hypertension, hyperlipidemia, diabetes, hyperuricemia, cerebrovascular disease, heart disease, kidney and urologic diseases, liver disease, gastrointestinal disease, endocrine disease, cancer.

RESULTS

Of the 4559 participants, 46.3% were men, and participants had a mean (SD) age of 60.9 (10.6) years (Table 1). The median (interquartile range) level of MVPA was 10.6 (0–46.2) MET-hours/week. A total of 55% engaged in the recommended level of MVPA (≥8.25 MET-hours/week), whereas 25.6% did not engage in any MVPA. Adults with greater MVPA were more likely to be men, older, smokers, less educated, less depressed, and more likely to have prevalent chronic diseases and history of low back or knee injury (all $P < 0.05$); however, MVPA was not associated with BMI ($P = 0.7$) (data not shown).

CLBP was present in 14.1% of adults ($n = 605$), CKP was present in 10.7%, and both pain conditions were present in 3.7%. Fair or poor self-rated health, history of injury, medication use, and consultation with physicians were significantly associated with CLBP (Table 2). The relationship between MVPA and CLBP was not significant ($P > 0.10$ for both linear and quadratic associations). Although CKP was more prevalent in adults with the lowest (0 MET-hours/week) and the highest (≥75.4 MET-hours/week) PA (10.8% and 12.2%, respectively) than in those with average PA (9.7% in those with 8.25–23.0 MET-hours/week), PRs adjusted for potential confounders including BMI (Model 2) were not significantly different from 1.00 (lowest MVPA: PR 1.12, 95% CI 0.84–1.50; highest PA: PR 1.26, 95% CI 0.93–1.70) (Table 3). The non-significant quadratic association between PA and CKP ($P = 0.08$) in Model 2, further attenuated (to $P = 0.17$) in Model 4 after additional adjustment for history of injury and pain management (ie, medication use and consultation) (Figure 1). The pattern of results were similar to the above results with CLBP and CKP evaluated separately when we evaluated CLBP and CKP together as a combined outcome (P quadratic trend > 0.3; data not shown).

Associations of age and history of injury with CLBP and CKP were found, but these associations attenuated when adjusted for medical treatment and consultation. A significant positive association of BMI with CKP, but not CLBP, persisted; per 5 kg/m^2, PRs were 1.03 (95% CI 0.91–1.17) for CLBP and 1.28 (95% CI 1.11–1.48) for CKP, based on Model 4 (Tables 2 and 3). History of injury was also associated with each CMP outcome: PR 1.60 (95% CI 1.35–1.90) for CLBP and PR 1.67 (95% CI 1.35–2.07) for CKP (Tables 2 and 3).

Table 2. Cross-sectional associations of energy expended on moderate to vigorous physical activity with chronic low back pain among Japanese adults ($n = 4559$)

	Adults with CLBP, %	PR (95% CI)[a]			
		Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
PA levels, MET-hours/week					
0	14.9	0.94 (0.72–1.23)	0.93 (0.71–1.22)	0.95 (0.73–1.24)	0.93 (0.72–1.21)
0.1–8.24	12.8	0.86 (0.66–1.13)	0.86 (0.65–1.13)	0.89 (0.68–1.18)	0.86 (0.66–1.13)
8.25–23.0	15.0	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
23.1–75.3	13.7	0.94 (0.68–1.31)	0.94 (0.67–1.30)	0.95 (0.69–1.32)	0.98 (0.72–1.33)
≥75.4	16.1	1.09 (0.84–1.41)	1.10 (0.851.42)	1.04 (0.80–1.35)	1.02 (0.79–1.32)
P for linearity		0.14	0.13	0.30	0.20
P for quadratic		0.29	0.28	0.53	0.87
Sex, female	13.2	0.99 (0.82–1.19)	1.01 (0.84–1.21)	1.07 (0.89–1.28)	0.93 (0.78–1.12)
Age					
50s	12.5	1.16 (0.88–1.52)	1.16 (0.88–1.52)	1.18 (0.90–1.55)	1.13 (0.86–1.49)
60s	14.0	1.33 (1.00–1.78)	1.34 (1.01–1.79)	1.39 (1.05–1.86)	1.19 (0.89–1.60)
70s	19.0	1.62 (1.19–2.20)	1.64 (1.21–2.24)	1.63 (1.20–2.23)	1.26 (0.92–1.74)
Self-rated health, fair or poor	30.3	2.59 (2.18–3.08)	2.59 (2.18–3.08)	2.36 (1.98–2.81)	1.75 (1.46–2.09)
Education years, per year	—[e]	0.98 (0.94–1.03)	0.99 (0.95–1.03)	0.99 (0.95–1.03)	1.01 (0.96–1.05)
Chronic disease history	15.6	1.03 (0.86–1.22)	1.01 (0.85–1.21)	1.01 (0.85–1.21)	1.03 (0.86–1.23)
Depressive symptom	15.2	1.06 (0.90–1.26)	1.07 (0.90–1.27)	1.01 (0.86–1.20)	1.03 (0.86–1.23)
Smoking					
Past smoker	18.2	1.29 (0.98–1.70)	1.30 (0.99–1.71)	1.23 (0.93–1.62)	1.17 (0.88–1.54)
Current smoker	15.9	1.23 (0.98–1.55)	1.25 (0.99–1.57)	1.21 (0.96–1.52)	1.14 (0.91–1.44)
BMI, per 5 kg/m^2	—[e]	—[f]	1.09 (0.97–1.23)	1.07 (0.95–1.22)	1.03 (0.91–1.17)
History of low back injury	27.6	—	—	2.38 (2.03–2.79)	1.60 (1.35–1.90)
Medication use for LBP	40.9	—	—	—	2.66 (2.17–3.27)
Consultation for LBP	39.8	—	—	—	1.88 (1.54–2.29)

BMI, body mass index; CI, confidence interval; CLBP, chronic low back pain; LBP, low back pain; MET, metabolic equivalent; PA, physical activity; PR, prevalence ratio.

[a]Model 1 adjusted for sex, age, education years, self-rated health, chronic disease history, depressive symptom, and smoking. Reference categories were male, 40s of age, excellent or good self-rated health, no chronic disease history, no depressive symptom, and never smoker. Linear and quadratic relationships were tested separately.

[b]Model 2 adjusted for variables in the Model 1 and BMI.

[c]Model 3 adjusted for variables in the Model 2 and history of joint injuries (two indicator variables for injury of the knee and of the low back; yes, no for each).

[d]Model 4 adjusted for variables in the Model 3 and pain management (medication use and consultation with physicians).

[e]Prevalence is not shown for continuous variable.

[f]Not included in the models.

The interaction between BMI and MVPA levels for CKP was not significant ($P > 0.9$ for linear and quadratic trends). When BMI and total MVPA levels were examined jointly, a non-significant U-shaped relationship between MVPA and CKP was observed in the high-BMI category (Model 4, Figure 2). The interaction between MVPA and joint injuries was also not significant ($P = 0.88$).

When we evaluated PA of different intensities, VPA, MPA, and walking were neither linearly nor non-linearly significantly associated with CLBP and CKP evaluated separately (all $P > 0.05$; data not shown) or with CLBP and CKP evaluated simultaneously as a combined outcome (Table 4).

All of these results from multiple imputed analyses were similar to those from complete-case analyses, with the exception of the complete-case analyses having less precision and wider confidence intervals; the variability of 5-time imputation was <10% of total variance (data not shown), while the variability due to multiple imputation was incorporated into estimations of precision and significant testing in all presented analyses.

DISCUSSION

This study examined the associations of PA with CLBP and CKP among middle-aged and older Japanese. We found that there were no significant cross-sectional relationships of PA with CLBP and CKP. While neither a U-shaped association nor interactions by body mass and prior injury were statistically significant, our analysis indicate the importance of accounting for body mass, history of injury, medication use, and consultation with physicians in research on PA and CMP.

Few previous studies have examined a potential non-linear relationship between PA and CMP, especially for CKP. Some studies suggested U-shaped relationships between PA and CLBP.[15,17,18] An occupational cohort study showed that the lowest and highest tertiles of minutes of MVPA yielded statistically significantly higher risks of low back pain than the middle tertile.[18] However, our cross-sectional investigation did not detect any significant linear or quadratic associations of PA and CLBP or CKP.

Table 3. Cross-sectional associations of energy expended on moderate to vigorous physical activity with chronic knee pain among Japanese adults (n = 4559)

	Adults with CKP, %	PR (95% CI)[a]			
		Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
PA levels, MET-hours/week					
0	10.8	1.15 (0.86–1.54)	1.12 (0.84–1.50)	1.14 (0.85–1.53)	1.14 (0.85–1.53)
0.1–8.24	9.9	1.02 (0.74–1.41)	0.99 (0.72–1.37)	0.98 (0.70–1.39)	0.98 (0.71–1.34)
8.25–23.0	9.7	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
23.1–75.3	10.3	1.09 (0.78–1.50)	1.06 (0.77–1.47)	1.03 (0.73–1.43)	0.97 (0.70–1.34)
≥75.4	12.2	1.26 (0.93–1.71)	1.26 (0.93–1.70)	1.19 (0.88–1.60)	1.15 (0.85–1.56)
P for linearity		0.53	0.43	0.79	1.00
P for quadratic		0.07	0.08	0.09	0.17
Sex, female	12.1	1.22 (0.98–1.52)	1.31 (1.05–1.64)	1.25 (1.00–1.56)	0.98 (0.79–1.22)
Age, years					
50s	8.0	1.85 (1.24–2.76)	1.88 (1.26–2.80)	1.84 (1.23–2.74)	1.51 (1.01–2.26)
60s	10.3	2.23 (1.49–3.32)	2.30 (1.54–3.44)	2.24 (1.50–3.34)	1.75 (1.16–2.62)
70s	19.1	3.77 (2.51–5.68)	4.14 (2.75–6.22)	3.56 (2.37–5.37)	2.06 (1.36–3.13)
Self-rated health, fair or poor	18.7	1.67 (1.36–2.06)	1.65 (1.34–2.03)	1.51 (1.22–1.86)	1.21 (0.98–1.49)
Education years	—[e]	0.96 (0.92–1.01)	0.97 (0.93–1.01)	0.97 (0.93–1.01)	1.01 (0.96–1.05)
Chronic disease history	12.7	1.18 (0.96–1.47)	1.07 (0.86–1.33)	1.06 (0.86–1.32)	0.98 (0.79–1.22)
Depressive symptom	11.2	1.19 (0.98–1.44)	1.24 (1.02–1.51)	1.20 (0.99–1.46)	1.17 (0.97–1.41)
Smoking					
Past smoker	11.1	1.11 (0.77–1.60)	1.15 (0.80–1.66)	1.17 (0.82–1.69)	1.17 (0.82–1.67)
Current smoker	6.0	0.73 (0.52–1.02)	0.78 (0.55–1.09)	0.80 (0.57–1.12)	0.87 (0.62–1.23)
BMI per 5 kg/m^2	—[e]	—[f]	1.68 (1.47–1.91)	1.57 (1.37–1.80)	1.28 (1.11–1.48)
History of knee injury	29.0	—	—	3.23 (2.65–3.94)	1.67 (1.35–2.07)
Medication use for KP	49.4	—	—	—	2.99 (2.29–3.89)
Consultation for KP	51.5	—	—	—	3.11 (2.44–3.96)

BMI, body mass index; CI, confidence interval; CKP, chronic knee pain; KP, knee pain; MET, metabolic equivalent; PA, physical activity; PR, prevalence ratio.

[a]Model 1 adjusted for sex, age, education years, self-rated health, chronic disease history, depressive symptom, and smoking. Reference categories were male, 40s of age, excellent or good self-rated health, no chronic disease history, no depressive symptom, and never smoker. Linear and quadratic relationships were tested separately.

[b]Model 2 adjusted for variables in the Model 1 and BMI.

[c]Model 3 adjusted for variables in the Model 2 and history of joint injuries (two indicator variables for injury of the knee and of the low back; yes, no for each).

[d]Model 4 adjusted for variables in the Model 3 and pain management (medication use and consultation with physicians).

[e]Prevalence is not shown for continuous variable.

[f]Not included in the models.

Both positive and negative effects of excess PA on knee joint are conceivable. A systematic review concluded that there was strong evidence for an inverse relationship between PA and cartilage defects of the knee joint.[51] However, the authors also concluded that there was a positive relationship between tibiofemoral osteophytes and PA. The results of previous studies on PA and joint health have been inconsistent, and many of the prior studies did not assess non-linear relationships or were too underpowered to do so.[51] Therefore, future longitudinal investigations examining a potential non-linear relationship between PA and CMP are of value.

Our results also showed the importance of taking into account BMI, past injuries, and factors related to pain management, which were all significantly associated with CMP. Higher BMI level in this study was significantly associated with higher prevalence of CKP but not CLBP, in line with the postulation that a greater body mass causes physical burden on the knee joint.[23] Our failure to show an interaction of PA and BMI on CKP may reflect the limited statistical power of the present study and also the limited range of BMI in our population, which predominantly comprised normal-weight adults with BMI < 25 kg/m^2 (80%). Only a few prior studies took a history of injury into account.[18,23] One third of the adults in our study reported a history of injury, and we observed a significant positive association of history of injury with CMP; it is possible that prior excess PA could have caused joint injury, which led to CMP. On the other hand, PA is recommended as a non-pharmacological intervention for CMP.[11,12] Thus, adults who had history of injury, and possibly CMP, might engage in more PA for treatment and rehabilitation.

Our results showed that there were strong associations of CMP with medication use and consultation with physicians and that adjusting for these factors attenuated the quadratic association between PA and CKP. As seeking medications and undergoing outpatient treatment is directly associated with not only pain but also PA, these results are plausible. Our findings thus emphasize that future research on the relationship between PA and CMP should consider effects of BMI, injury, and pain management factors.

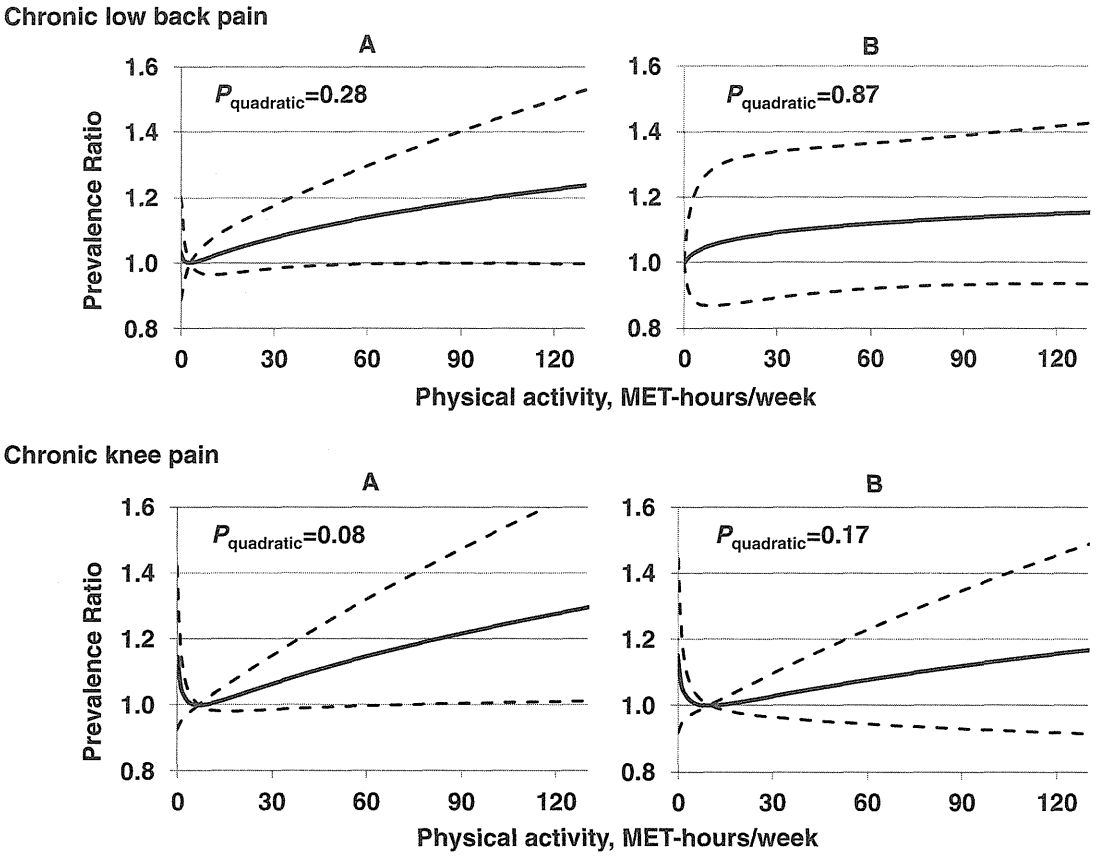

Figure 1. Associations between moderate-to-vigorous physical activity and the prevalence of chronic low back pain and chronic knee pain among Japanese adults (n = 4559). Solid lines represent prevalence ratios (PRs), and dashed lines indicate 95% confidence intervals estimated by Poisson regression, estimated by a quadratic function of physical activity levels (metabolic equivalent of task [MET]-hours/week). Panels on the left (A) display PR adjusted for sex, age, education years, self-rated health, depressive symptoms, smoking habit, chronic disease history, and body mass index; while on the right (B), PRs are further adjusted for history of joint injuries, medication use, and consultation with physicians for pain management. The reference value for each was fixed to the values giving the lowest prevalence of each outcome. P for each quadratic function is displayed.

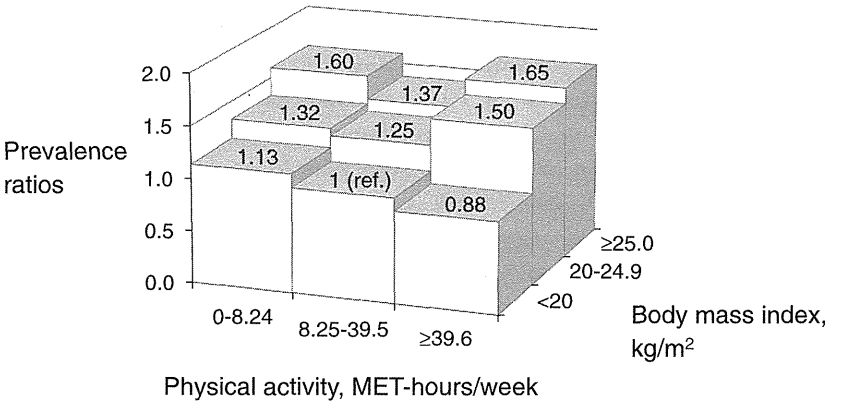

Figure 2. Associations of moderate-to-vigorous physical activity (metabolic equivalent of task [MET]-hours/week) and weight status with chronic knee pain among Japanese adults (n = 4559). Prevalence ratios were estimated with adjustment for sex, age, education years, self-rated health, depressive symptoms, smoking habit, chronic disease history, past joint injuries, medication use, and consultation with physicians for pain management. After adjustment, no significant prevalence ratios were observed (all $P > 0.05$). Interactions between body-mass index and physical activity levels in models, considering linear as well as non-linear associations, were also not significant (all $P > 0.1$).

Table 4. Cross-sectional associations between physical activity of different intensity and either chronic low back pain or chronic knee pain among Japanese adults (n = 4559)

Physical activity type	n	PR (95% CI)[a]			
		Model 1[b]	Model 2[c]	Model 3[d]	Model 4[e]
Vigorous PA, min/week					
0	3200	1.13 (0.80–1.59)	1.15 (0.81–1.63)	1.15 (0.83–1.59)	1.15 (0.91–1.45)
>0–40.6	453	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
40.9–180	458	1.27 (0.84–1.90)	1.26 (0.83–1.90)	1.18 (0.80–1.75)	1.19 (0.91–1.57)
>180	448	1.05 (0.67–1.66)	1.06 (0.67–1.67)	0.98 (0.64–1.49)	0.93 (0.67–1.29)
$P_{linearity}$[f]		0.94	0.89	0.43	0.21
$P_{non\text{-}linearity}$[f]		0.93	0.83	0.97	0.45
Moderate PA, min/week					
0	2990	1.05 (0.80–1.38)	1.02 (0.78–1.33)	1.04 (0.82–1.32)	1.16 (0.88–1.53)
>0–58.8	504	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
60.0–240	558	1.20 (0.87–1.65)	1.20 (0.88–1.63)	1.16 (0.87–1.55)	1.28 (0.96–1.69)
>240	507	1.13 (0.82–1.54)	1.14 (0.84–1.55)	1.13 (0.85–1.51)	1.29 (0.91–1.82)
$P_{linearity}$[f]		0.18	0.07	0.17	0.22
$P_{non\text{-}linearity}$[f]		0.56	0.61	0.52	0.28
Walking, min/week					
0	1271	1.10 (0.92–1.32)	1.11 (0.93–1.34)	1.09 (0.90–1.31)	1.08 (0.91–1.29)
>0–119	1055	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
120–404	1053	1.03 (0.85–1.25)	1.04 (0.86–1.26)	1.04 (0.86–1.26)	1.06 (0.88–1.26)
>404	1180	1.11 (0.91–1.36)	1.12 (0.91–1.38)	1.11 (0.90–1.36)	1.13 (0.93–1.36)
$P_{linearity}$[f]		0.99	0.98	0.84	0.57
$P_{non\text{-}linearity}$[f]		0.08	0.06	0.13	0.18

CI, confidence interval; PA, physical activity; PR, prevalence ratio.

[a]Prevalence ratios (PR) and 95% confidence intervals were estimated by Poisson regression. We examined chronic low back pain (CLBP), chronic knee pain (CKP), or both as the outcome of interest simultaneously by generalized estimating equation that accounted for the correlations between CLBP and CKP (kappa = 0.20). The models also included all PA measures simultaneously. Correlations among these PA categories were moderate (Spearman r = 0.48 between vigorous and moderate PA; 0.31 between vigorous PA and walking; 0.28 between moderate PA and walking). For each type of physical activity, we categorized adults into four groups by treating adults with 0 min/week as a single category and by splitting the others into tertiles.

[b]Model 1 adjusted for sex, age, education years, self-rated health, chronic disease history, depressive symptom, and smoking.

[c]Model 2 adjusted for variables in the Model 1 and body mass index.

[d]Model 3 adjusted for variables in the Model 2 and history of joint injuries (two indicator variables for injury of the knee and of the low back; yes or no for each).

[e]Model 4 adjusted for variables in the Model 3 and pain management (medication use and consultation with physicians).

[f]Log-linear and quadratic relationships were tested separately, using log-transformed variables.

Globally, disability due to musculoskeletal disorders is estimated to have increased by 45% from 1990 to 2010, related to the aging of the population.[2] It remains unknown what the most effective and affordable strategies are to reduce the global burden of musculoskeletal disorders.[52] Although we detected little indication of benefits of PA for CMP, potential beneficial effects of PA on CMP still deserve discussion. Possible pathways linking greater PA to a reduced risk of CMP include but are not limited to reduction of mechanical stress through improving muscle strength, range of movement, and joint structure; improvement of blood flow to painful regions; relief of psychological stress, such as distraction and depression[7,53–55]; and elevation of tolerance to pain associated with increased serum concentrations of endocannabinoids that reduce pain sensation.[56] Our community-based research in Japan, which has one of the most aged societies in the world, provides important insights into the studies on PA and musculoskeletal health.

Our study has several limitations. In our cross-sectional study, reverse causation and recall bias might have occurred. Individuals with CMP may reduce levels of recreational PA and PA intensities, leading to null findings for MVPA and CMP. Limitations are likely to be present in our assessment of injury, because this was ascertained retrospectively. We also had a limited sample size to tease out independent relations among PA levels, CMP, and potential confounders. Future research should adopt a longitudinal design, assessing PA prior to the development of injuries or pains. Considering potential biases due to self-reported PA, objective measures of PA, as well as anthropometrics, injuries, and pain, should be incorporated in future research.

In conclusion, this cross-sectional study showed that there were no significant linear or quadratic relationships of PA with CLBP and CKP. Our findings indicate the importance of evaluating PA, CMP, body mass, injuries, and pain management factors simultaneously.

ONLINE ONLY MATERIALS

eQuestionnaire 1. Musculoskeletal pain questionnaire. Abstract in Japanese.

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Conflicts of interest: None declared.

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RESEARCH PAPER

Strong influence of dietary intake and physical activity on body fatness in elderly Japanese men: age-associated loss of polygenic resistance against obesity

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Abstract Genome-wide association studies identified single nucleotide polymorphisms (SNPs) associated with body mass index (BMI) in middle-aged populations; however, it is unclear whether these SNPs are associated with body fatness in elderly people. We examined the association between genetic risk score (GRS) from BMI-associated SNPs and body fatness in elderly Japanese men. We also examined the contribution of GRS, dietary macronutrient intake, and physical activity to body fatness by different age groups. GRS was calculated from 10 BMI-associated SNPs in 84 middle-aged (30–64 years) and 97 elderly (65–79 years) Japanese men; subjects were divided into low, middle, and high GRS groups. Dietary macronutrient intake was assessed using a questionnaire, and physical activity was evaluated using both a questionnaire and an accelerometer. The middle-aged individuals with a high GRS had greater BMI; waist circumference; and total abdominal fat, visceral fat, and subcutaneous fat areas than the middle-aged individuals with low GRS, whereas the indicators were not different between the GRS groups in elderly individuals. Multiple linear regression analysis showed that GRS was the strongest predictor of BMI, total abdominal fat, and visceral fat in the middle-aged group, whereas fat, alcohol, and protein intakes or vigorous-intensity physical activity were more strongly associated with these indicators than was GRS in the elderly group. These results suggest that GRS from BMI-associated SNPs is not predictive of body fatness in elderly Japanese men. The stronger contribution of dietary macronutrient intake and physical activity to body fatness may attenuate the genetic predisposition in elderly men.

Keywords Body fatness · Aging · SNP · Genetic risk score · Dietary macronutrient intake · Physical activity

Introduction

The prevalence of obesity in elderly populations is increasing worldwide, including in Asian countries (Popkin and Doak 1998). Obesity and abdominal adiposity increases the risk of cardiometabolic diseases, sarcopenic obesity, and functional disability even in the elderly Asian individuals who generally have a lower body mass index (BMI) than European people (Kim et al. 2009; Ochi et al. 2010; WHO Expert Consultation 2004). Therefore, identifying the determinants of obesity in elderly Asian individuals is important to prevent obesity and to reduce the burden of health care in a rapidly aging society in Asia.

Genetic variation is an important determinant of susceptibility to obesity. Recent genome-wide association studies (GWASs) identified single nucleotide polymorphisms (SNPs) at several genetic loci that are associated with BMI in European and Asian populations (Thorleifsson et al. 2009;

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Wen et al. 2012; Willer et al. 2009). Several studies calculated the genetic risk score (GRS) from the number of risk alleles of GWAS-derived SNPs to examine the polygenic effect of these variants and demonstrated that the GRS is strongly associated with BMI (Cheung et al. 2010; Peterson et al. 2011; Renstrom et al. 2009). However, most of these BMI-associated SNPs were identified in the cohorts consisting of mainly middle-aged individuals; therefore, it is unclear whether these SNPs and GRS are also associated with BMI and indices of adiposity in elderly people.

Interestingly, a recent study reported that the SNPs previously associated with BMI in middle-aged populations and GRS constructed from these variants were not associated with body weight or body fatness in the older European and African-American populations (Murphy et al. 2013). In that study, Murphy et al. further suggested that an increase in body weight from midlife to old age might underlie the weak associations between SNPs and body fatness. However, in contrast to European and African individuals, Asian people generally maintain their body weight from midlife to later life (Funatogawa et al. 2009). Therefore, BMI-associated SNPs identified in middle-aged populations may be associated with BMI and other indicators of body fatness in the elderly Asian populations.

Moreover, not only genetic factors, but also environmental factors including lifestyle, such as dietary intake and physical activity, are associated with obesity (Donnelly et al. 2009; Mozaffarian et al. 2011); however, Murphy et al. did not examine the association of SNPs with body weight in relation to environmental factors. Twin studies demonstrated that the contribution of genetic factors to body weight might decrease with advancing age (Carmichael and Mcgue 1995; Korkeila et al. 1991). Alternatively, environmental factors may have stronger effects on body weight because the genetic influence lessens when people become older. Therefore, it should be examined whether the contribution of environmental factors to body fatness is different between middle-aged and elderly individuals.

In the present study, we calculated GRS on the basis of BMI-associated SNPs previously identified in middle-aged Asian populations. We examined whether GRS is associated with indicators of body fatness in middle-aged and elderly Japanese men, respectively. We also examined whether the contribution of GRS, dietary macronutrient intake, and physical activity to body fatness differ by age groups.

Materials and Methods

Subjects

Eighty-four middle-aged (30–64 years) and 97 elderly (65–79 years) Japanese men participated in this study. All subjects were free from endocrine disorders that might affect their body weight (e.g., Cushing disease, hypothyroidism, hypothyroidism). Subjects also did not take any medications that might affect energy expenditure (e.g., steroids, thyroid hormones). Diabetes status was defined in accordance with World Health Organization criteria (Alberti et al. 1998); 11 subjects (6.1 %) had type 2 diabetes. Current/former smoking status was assessed with a questionnaire. All subjects provided written informed consent before enrollment in the study, which was approved by the Ethical Committee of Waseda University. The study was conducted in accordance with the Declaration of Helsinki.

Anthropometric characteristics

Body weight and body fat percentages (assessed by bioelectrical impedance analysis) were measured using an electronic scale (InnerScan BC-600, Tanita Inc., Tokyo, Japan), whereas height was measured with a stadiometer (YL-65, YAGAMI Inc., Nagoya, Japan). BMI was calculated from measurements of body weight and height. Waist circumference was measured at the umbilical region with an inelastic measuring tape. The total abdominal fat, visceral fat, and subcutaneous fat areas were measured using magnetic resonance imaging (Signa 1.5 T, General Electric Inc., Milwaukee, WI, USA). The imaging conditions included a T1-weighted spin-echo and axial-plane sequence with a slice thickness of 10 mm, a repetition time of 140 ms, and an echo time of 12.3 ms (Usui et al. 2010). Cross-sectional images were scanned at the umbilical region. During the scan, the subjects were asked to hold their breath for approximately 30 s after inhalation to reduce respiratory motion artifacts. The magnetic resonance images were transferred to a personal computer in the Digital Imaging and Communications in Medicine file format, and the cross-sectional area of the visceral fat at the umbilical region was determined using image-analysis software (sliceOmatic 4.3 for Windows, TomoVision, Montreal, Quebec, Canada). To minimize interobserver variation, the same investigator performed all analyses; the coefficient of variation was 0.4 % for the cross-sectional areas of the umbilical region.

Physical activity

Physical activity was measured using a uniaxial accelerometer (Kenz Lifecorder EX, SUZUKEN Co Ltd., Nagoya, Japan). Instructions for the accelerometer were given to the subjects before the test period; they were told to continuously wear it on their belt or waistband at the right midline of the thigh for 10 days, except when sleeping or bathing. Moderate-intensity physical activity (MPA) and vigorous-

intensity physical activity (VPA) were used as the indices of physical activity. On a scale with the points 0, 0.5, and 1–9, the Lifecorder system determined the level of physical activity intensity every 4 s. As described previously (Kumahara et al. 2004), the amount of time spent at intensity levels 4–6 and 7–9 were used as the amount of time spent in MPA and VPA, respectively. We also calculated the time spent in moderate- and vigorous-intensity physical activity (MVPA) from MPA and VPA. Subjects recorded leisure time physical activities performed during 10 days in a questionnaire, because several types of activity such as swimming, cycling, and rowing cannot be assessed by an accelerometer. We calculated self-reported time spent in MPA and VPA based on the metabolic equivalents (METs) of each activity (Ainsworth et al. 2000); MPA was defined as 3.0–5.9 METs and VPA as ≥6.0 METs. When an accelerometer indicated intensity levels 0 or 0.5 at the periods that subjects reported as being engaged in MPA or VPA in the questionnaire, we added the time spent in MPA and VPA to the accelerometer-measured MPA and VPA. Total energy expenditure was also assessed through a combination of an accelerometer and a questionnaire such as a MPA and VPA assessment. Valid physical activity data were obtained from 79 (94.0 %) middle-aged and 94 (96.9 %) elderly subjects and analyzed.

Dietary assessment

Dietary intake was assessed using a brief self-administered diet history questionnaire (BDHQ). The BDHQ is a 4-page questionnaire that yields information on consumption frequency of selected foods to estimate the dietary intake of 58 food and beverage items (Kobayashi et al. 2011). The validity of the nutrient intake data assessed with the BDHQ was confirmed using semi-weighed 16-day dietary records as a reference (Kobayashi et al. 2012). On the basis of the total daily energy intake and dietary macronutrient intake assessed using the BDHQ, we calculated the percentage of energy intake from carbohydrates, fat, protein, and alcohol.

Collection and analysis of blood samples

Blood samples were collected between 8:30 and 11:00 a.m. after a 12-h overnight fast and then centrifuged at 3,000×*g* for 15 min at 4 °C. Serum and plasma were stored at −80 °C until the time of analysis. Concentrations of HDL cholesterol, LDL cholesterol, triglycerides, and fasting glucose were determined using standard enzymatic techniques (BML, Inc., Tokyo, Japan). Glycated hemoglobin (HbA1c) levels were determined using the latex coagulation method (BML, Inc.).

SNP selection

Ten BMI-associated SNPs were selected for this study. All selected SNPs met the following criteria: (1) a significant genome-wide association ($p < 5.0 \times 10^{-8}$) in any GWAS of European-descent populations (Thorleifsson et al. 2009; Willer et al. 2009), (2) a suggestive association ($p < 1.0 \times 10^{-4}$) in the meta-analysis in Asian populations (Wen et al. 2012), and (3) the minor allele frequency (MAF) in the Japanese population was ≥0.05. *SEC16B* rs574367, *TMEM18* rs11127485, *TFAP2B* rs4715210, and *MC4R* rs6567160 were not included in the SNP array in the present study; these were replaced with rs543874, rs2867125, rs987237, and rs10871777, all of which are in strong linkage disequilibrium with the original SNPs, respectively ($D' = 1.0$, $r^2 > 0.7$, in HapMap JPN). All of the SNPs were in Hardy–Weinberg equilibrium ($p > 0.001$) and their MAF was ≥0.05 in our study population (Table 1).

SNP genotyping

Nuclear DNA was extracted from peripheral blood using the QIAamp DNA Mini kit (QIAGEN, Hilden, Germany); DNA quality was evaluated using agarose gel electrophoresis and spectrophotometry. We confirmed that none of the DNA samples was fragmented and that the A260/A280 ratio was 1.8–2.0. SNP genotyping was performed by using the Infinium HumanExome BeadChip version 1.1 (Illumina, Inc., San Diego, CA, USA) according to the manufacturer's protocol. Genotype calling was performed using the GenTrain clustering algorithm (version 1.0) in the GenomeStudio (ver. 2011.1; Illumina, Inc.). Cluster boundaries were determined using the standard cluster files provided by Illumina. The SNP call rate was at least 98.7 % for all samples.

Calculation of GRS

We calculated GRS according to the 10 selected SNPs. We assumed that each SNP acts in an additive manner, and the GRS was calculated using a weighted method (Cheung et al. 2010; Renstrom et al. 2009; Tanisawa et al. 2014). Each SNP was weighted by its effect size per allele on BMI (in percentage of the SD) derived from a meta-analysis in Asian populations (Wen et al. 2012). The weighted scores for each SNP were calculated by multiplying each effect size by the number of corresponding risk alleles. These scores were totaled to obtain a GRS for each subject. We divided subjects into the low, middle, and high GRS groups according to the tertile of a GRS. The range for each GRS group was as follows: low: 10–30; middle: 31–38; and high: 39–67.

Table 1 SNPs selected to calculate GRS

SNP	Gene symbol	Chromosome	Base pair position (GRCh37.p10)	Allele (M/m)	Risk allele	MAF	β*	HWE *p*
rs543874	*SEC16B*	1	177889480	A/G	G	0.22	6.57	0.662
rs2867125	*TMEM18*	2	622827	C/T	C	0.08	5.05	0.614
rs713586	*ADCY3*	2	25158008	T/C	C	0.46	2.94	0.457
rs10938397	*GNPDA2*	4	45182527	A/G	G	0.33	3.71	0.091
rs987237	*TFAP2B*	6	50803050	A/G	G	0.25	3.84	0.847
rs6265	*BDNF*	11	27679916	T/C	C	0.40	4.53	0.537
rs2241423	*MAP2K5*	15	68086838	A/G	G	0.33	3.10	1.000
rs17817449	*FTO*	16	53813367	T/G	G	0.19	8.46	0.144
rs10871777	*MC4R*	18	57851763	A/G	G	0.24	5.64	0.223
rs3810291	*TMEM160*	19	47569003	A/G	A	0.23	3.48	0.003

GRS genetic risk score, *HWE* Hardy–Weinberg equilibrium, *M* major allele, *m* minor allele, *MAF* minor allele frequency, *SNP* single nucleotide polymorphism

* Effect of SNPs per allele on BMI (in percentage of the SD) derived from the meta-analysis (Wen et al. 2012)

Statistical analysis

All statistical analyses were performed with SPSS, version 21.0 (SPSS, Inc., Chicago, IL, USA), or PLINK, version 1.07 (Massachusetts General Hospital, Boston, MA, USA). The allelic frequencies of the selected SNPs were calculated using a gene-counting method, and the Hardy–Weinberg equilibrium and linkage disequilibrium for each SNP were assessed by the Chi-square test. Student's *t* test (for normally distributed variables), Mann–Whitney *U* test (for non-normally distributed variables), or the Chi-square test (for categorical variables) was used to evaluate the differences between the middle-aged and elderly groups. The differences in the indicators of body fatness among age groups and GRS groups were assessed by two-way analysis of covariance (ANCOVA) adjusted for age, current/former smoking status, and type 2 diabetes. A post hoc test with Bonferroni correction was used to identify significant differences among mean values if a significant main effect or interaction was identified. Multiple linear regression analysis was performed to examine the associations of GRS, dietary macronutrient intake, and physical activity with indicators of body fatness in the middle-aged and elderly groups, respectively. All measurements and calculated values are presented as mean ± SD (for normally distributed variables) or medians (interquartile range) (for non-normally distributed variables). The level of significance was set at $p < 0.05$.

Results

Subject characteristics

The characteristics of the study subjects are shown in Table 2. Height, body weight, and total energy expenditure were lower in the elderly group than in the middle-aged group ($p < 0.05$). Fasting glucose and HbA1c levels were higher in the elderly group than in the middle-aged group ($p < 0.05$).

Association among age groups, GRS groups, and indicators of body fatness

We compared the indicators of body fatness among different age groups and GRS groups. Two-way ANCOVA adjusted for age, current/former smoking status, and type 2 diabetes detected a significant interaction effect between age groups and GRS groups on body weight, BMI, waist circumference, total abdominal fat, visceral fat, and subcutaneous fat. BMI and waist circumference were significantly higher in the high and middle GRS groups than in the low GRS group only among the middle-aged group (Fig. 1a; Table 3, $p < 0.05$), whereas no significant difference was observed in BMI and waist circumference among different GRS groups in the elderly group. Furthermore, the middle-aged individuals with a high GRS had higher body weight, total abdominal fat, visceral fat, and subcutaneous fat than middle-aged individuals with a low GRS (Fig. 1b; Table 3, $p < 0.05$); however, these values were not different between the GRS group in the elderly group.

Contribution of GRS, physical activity, and dietary macronutrient intake to body fatness in middle-aged and elderly men

Because the relationship of GRS groups with indicators of body fatness differed by age groups, we performed multiple linear regression analysis to examine the strength of contributions of GRS, physical activity, and dietary macronutrient intake to body fatness in the middle-aged and elderly groups (Table 4). We selected GRS, VPA, fat intake, protein intake, and alcohol intake as independent variables, and BMI, total abdominal fat, and visceral fat as dependent variables. When we entered carbohydrate

Table 2 Characteristics of the subjects ($n = 181$)

	Middle-aged	Elderly	p^*
n	84	97	
Age (year)	53.4 ± 11.4	70.0 ± 3.9	**<0.001**
Height (cm)	171.1 ± 5.8	168.5 ± 7.1	**0.007**
Body weight (kg)	70.2 ± 9.5	66.7 ± 9.0	**0.012**
BMI (kg/m^2)	23.9 ± 2.7	23.4 ± 2.3	0.172
Body fat (%)	20.0 ± 4.8	21.0 ± 4.3	0.145
Waist circumference (cm)	84.0 ± 8.2	85.1 ± 6.7	0.325
Total abdominal fat (cm^2)	223.2 ± 93.0	230.0 ± 73.6	0.592
Visceral fat (cm^2)	106.0 ± 49.4	116.9 ± 47.6	0.131
Subcutaneous fat (cm^2)	117.2 ± 54.6	113.1 ± 39.5	0.561
HDL cholesterol (mg/dL)	57.0 (50.0–68.0)	61.0 (51.3–68.0)	0.376
LDL cholesterol (mg/dL)	121.5 ± 30	122.7 ± 28.3	0.784
Triglycerides (mg/dL)	95.0 (67.0–127.0)	83.5 (65.0–116.0)	0.253
Fasting glucose (mg/dL)	95.0 (88.0–101.0)	98.0 (93.0–105.0)	**0.002**
HbA1c (%)	4.9 (4.8–5.0)	4.9 (5.0–5.2)	**0.006**
Total energy expenditure (kcal/day)†	2342 ± 244	2121 ± 263	**<0.001**
MPA (min/day)†	40.0 (27.0–55.0)	41.0 (21.5–55.0)	0.786
VPA (min/day)†	6.0 (1.0–13.0)	2.0 (0.0–11.0)	0.081
MVPA (min/day)†	51.0 (34.0–68.0)	50.5 (27.8–68.3)	0.778
Total energy intake (kcal/day)	2150 ± 653	2213 ± 627	0.509
Carbohydrate intake (% energy)	51.0 ± 7.7	50.9 ± 8.4	0.870
Fat intake (% energy)	25.6 ± 5.1	24.6 ± 5.6	0.204
Protein intake (% energy)	15.1 ± 2.7	15.0 ± 2.6	0.956
Alcohol intake (% energy)	5.7 (2.3–13.7)	7.8 (2.4–13.4)	0.583
Current/former smoking status (%)	42.9	51.5	0.243
Type 2 diabetes (%)	2.4	9.3	0.053

Data are mean ± SD or median (interquartile range) values. Data were analyzed using Student's *t* test (for normally distributed variables), Mann–Whitney *U* test (for non-normally distributed variables), or Chi-square test (for categorical variables)

BMI body mass index, *HbA1c* glycated hemoglobin, *MPA* moderate-intensity physical activity, *MVPA* moderate- and vigorous-intensity physical activity, *VPA* vigorous-intensity physical activity

Boldface indicates significance ($p < 0.05$)

* Middle-aged vs. elderly

† Middle-aged: $n = 79$; elderly: $n = 94$

intake, fat intake, and alcohol intake into the models simultaneously, the variance inflation factors exceeded 10; therefore, we excluded carbohydrate intake from the models. In the middle-aged group, GRS was the strongest predictor of BMI ($p < 0.001$), total abdominal fat ($p = 0.001$), and visceral fat ($p = 0.003$). On the other hand, other dietary macronutrient intake and VPA were not associated with any indicators of body fatness, although alcohol intake was associated with visceral fat ($p = 0.024$). In contrast to the middle-aged group, high fat intake was the strongest predictor of increased BMI ($p = 0.037$), total abdominal fat ($p = 0.001$), and visceral fat ($p < 0.001$) in the elderly group; however, GRS was not associated with any indicators. Additionally, both low VPA and high alcohol intake were associated with increased total abdominal fat and visceral fat ($p < 0.05$, respectively); low protein intake was also associated with increased visceral fat ($p = 0.037$). We also entered MVPA into the models instead of VPA; however, MVPA was not associated with indicators of body fatness in either the middle-aged or the elderly group.

Discussion

The main finding of the present study is that GRS from BMI-associated SNPs previously identified in the middle-aged populations is not associated with any indicator of body fatness in elderly Japanese men, even though it is a strong predictor of body fatness in middle-aged Japanese men. We also demonstrated that the strength of the contributions of dietary macronutrient intake and physical activity to body fatness differed by the age group, which may explain in part the dissociation of the genetic influence on body fatness in the elderly individuals.

In accordance with our finding, a study recently reported that the SNPs previously associated with BMI in the middle-aged populations were not associated with body weight and adiposity in older European and African-American populations (Murphy et al. 2013). In the subjects participating in the longitudinal study, an average weight gain from midlife to old age was about 5 %, and only one-third of the subjects maintained body weight within 5 % (Murphy et al. 2013). It was also reported that age-related

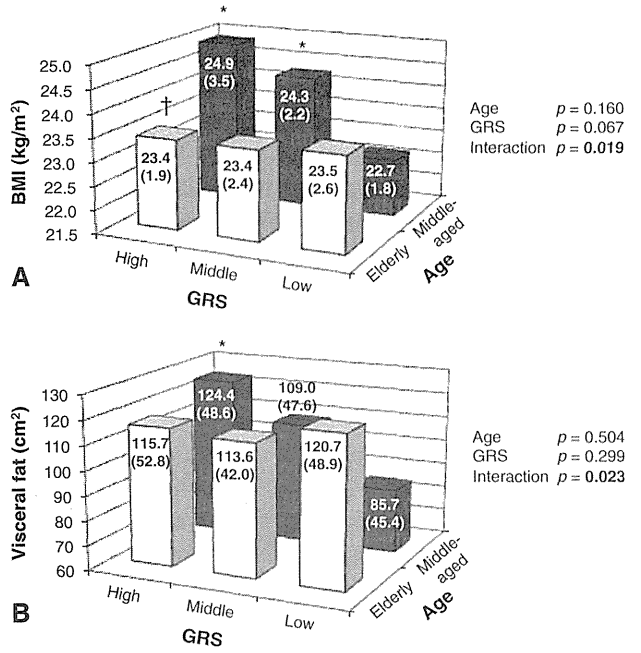

Fig. 1 BMI (**a**) and Visceral fat (**b**) among age groups and GRS groups. Data are presented as mean (SD) values. Data were analyzed using two-way ANCOVA adjusted for age, current/former smoking status, and type 2 diabetes. $*p < 0.05$ versus the low GRS group within the same age group. $\dagger p < 0.05$ versus the middle-aged group within the same GRS group. *Boldface* indicates significance ($p < 0.05$). *BMI* body mass index, *GRS* genetic risk score

body composition and fat distribution changes occur even in weight-stable elderly individuals (Zamboni et al. 2003). These age-related anthropometric changes were suggested to account for the dissociation between BMI-associated SNPs with adiposity in elderly individuals. However, the indicators of body fatness including BMI, body fat percentage, waist circumference, total abdominal fat, visceral fat, and subcutaneous fat were not statistically different between the middle-aged and elderly Japanese individuals in the present study. This suggests that null associations of BMI-associated SNPs with indicators of body fatness may not be explained by changes in body weight and body composition from midlife to old age and are likely common phenomena among various ethnic populations.

Our data have demonstrated that dietary macronutrient intake and physical activity are more strongly associated with body fatness in the elderly than in the middle-aged, suggesting that the relative contributions of genetic and environmental factors to body fatness differ by age groups. Among the dietary factors, fat intake was the most robustly associated with BMI, total abdominal fat, and visceral fat in elderly individuals. Many studies reported that the percentage of energy intake from fat is strongly associated with obesity in Western countries (Bray and Popkin 1998; Dreon et al. 1988). In contrast, no relationship between fat intake and BMI was observed in young Japanese women or

Table 3 Association among age groups, GRS groups, and indicators of body fatness ($n = 181$)

Age group	Middle-aged (30–64 years)			Elderly (65–79 years)			Age	GRS	Interaction
GRS	Low	Middle	High	Low	Middle	High	*p*	*p*	*p*
n	30	25	29	37	31	29			
Age (year)	52.5 ± 11.8	54.0 ± 11.9	53.7 ± 10.8	69.0 ± 3.5	70.0 ± 3.9	71.3 ± 3.9	**<0.001**	0.473	0.881
Body weight (kg)	66.3 ± 5.9	72.0 ± 8.3	72.7 ± 12.2*	67.4 ± 9.7	65.4 ± 8.2	67.1 ± 9.1	0.282	0.152	**0.047**
BMI (kg/m²)	22.7 ± 1.8	24.3 ± 2.2*	24.9 ± 3.5*	23.5 ± 2.6	23.4 ± 2.4	23.4 ± 1.9†	0.160	0.067	**0.019**
Body fat (%)	18.5 ± 4.2	20.4 ± 4.8	21.1 ± 5.1	21.5 ± 4.9	20.7 ± 4.7	20.6 ± 3.1	0.715	0.722	0.059
Waist circumference (cm)	80.2 ± 6.8	85.9 ± 7.0*	86.3 ± 9.1*	85.6 ± 7.2	84.3 ± 6.5	85.3 ± 6.3	0.310	0.125	**0.010**
Total abdominal fat (cm²)	183.0 ± 79.9	231.9 ± 85.7	257.4 ± 98.5*	239.6 ± 80.3†	226.8 ± 70.5	221.2 ± 68.8	0.782	0.234	**0.005**
Visceral fat (cm²)	85.7 ± 45.4	109.0 ± 47.6	124.4 ± 48.6*	120.7 ± 48.9	113.6 ± 42.0	115.7 ± 52.8	0.504	0.299	**0.023**
Subcutaneous fat (cm²)	97.4 ± 40.3	122.9 ± 53.6	133.0 ± 63.0*	118.9 ± 45.4†	113.2 ± 41.3	105.5 ± 27.8	0.847	0.332	**0.012**

Data are mean ± SD values. Data were analyzed by two-way ANCOVA adjusted for age, current/former smoking status, and type 2 diabetes

BMI body mass index, *GRS* genetic risk score

Boldface indicates significance ($p < 0.05$)

* $p < 0.05$ versus the low GRS group within the same age group

† $p < 0.05$ versus middle-aged group within the same GRS group

Table 4 Multiple linear regression analysis with BMI, total abdominal fat, and visceral fat as dependent variables ($n = 173$)

	BMI		Total abdominal fat		Visceral fat	
	β	*p*	β	*p*	β	*p*
Middle-aged ($n = 79$)						
GRS	**0.491**	**<0.001**	**0.382**	**0.001**	**0.321**	**0.003**
VPA (min/day)	0.003	0.973	−0.048	0.653	−0.061	0.554
Fat intake (% energy)	0.119	0.341	0.152	0.245	0.107	0.399
Protein intake (% energy)	0.180	0.130	0.174	0.160	0.176	0.144
Alcohol intake (% energy)	0.084	0.455	0.115	0.328	**0.262**	**0.024**
Model r^2	**0.301**	**0.001**	**0.235**	**0.008**	**0.276**	**0.001**
Elderly ($n = 94$)						
GRS	0.035	0.752	−0.049	0.633	0.004	0.968
VPA (min/day)	−0.166	0.124	**−0.232**	**0.024**	**−0.198**	**0.046**
Fat intake (% energy)	**0.303**	**0.037**	**0.460**	**0.001**	**0.520**	**<0.001**
Protein intake (% energy)	−0.103	0.457	−0.243	0.063	**−0.267**	**0.037**
Alcohol intake (% energy)	0.103	0.404	**0.231**	**0.048**	**0.399**	**0.001**
Model r^2	0.082	0.453	**0.187**	**0.016**	**0.231**	**0.002**

All models were adjusted for age, current/former smoking status and type 2 diabetes

Boldface indicates significance ($p < 0.05$)

β standardized coefficient, *BMI* body mass index, *GRS* genetic risk score, *VPA* vigorous-intensity physical activity

young and middle-aged Chinese populations in which fat intake was relatively low (mean 29.4 and 24.8 %, respectively) (Sasaki et al. 2003; Stookey 2001). Although several lines of evidence is available regarding the effect of fat intake on body fatness in elderly people, reduced fat oxidation is suggested to explain susceptibility to fat accumulation in this group (Levadoux et al. 2001; Rising et al. 1996). This age-related change in energy metabolism may contribute to the strong association between fat intake and body fatness only in elderly individuals despite a relatively low percentage of energy intake from fat. Moreover, high protein intake was also associated with low visceral fat only in elderly individuals. Several studies demonstrated that adequate protein intake prevents age-related muscle loss (Genaro and Martini 2010; Houston et al. 2008). Decline in muscle mass is closely related to visceral adiposity in elderly people (Song et al. 2004; Yamada et al. 2014), which may explain the relationship between high protein intake and low visceral fat in the present study.

Furthermore, a high level of VPA was associated with low total abdominal fat and visceral fat in elderly individuals. Total energy expenditure of physical activity seems to be important for body weight control; however, the benefit of VPA independent from the total volume of activity was documented in several studies. For example, it was demonstrated that high-intensity exercise training induced a greater decrease in subcutaneous skinfolds than low-intensity exercise training, even though training-induced energy expenditure was about half that in low-intensity exercise training (Tremblay et al. 1994). High-intensity exercise is associated with increased energy expenditure and fat oxidation at a resting state (Treuth et al. 1995, 1996); therefore, VPA may strongly influence body fatness, especially in elderly people with a decreased metabolic rate.

Nevertheless, the total coefficient of determination (model r^2) for BMI was not significant in the elderly, even though model r^2 for total abdominal fat and visceral fat was comparable between the middle-aged and elderly groups. It suggests that dissociation between GRS and BMI cannot be explained by dietary macronutrient intake and physical activity only. Although BMI is widely used as an indicator of body fatness, it is also associated with total muscle mass in older people (Iannuzzi-Sucich et al. 2002; Kanehisa and Fukunaga 2013). Therefore, genetic factors associated with muscle mass may greatly contribute to individual variations in BMI in the elderly. We should also consider environmental factors in early life. The elderly individuals participating in the present study were born around World War II when Japan faced serious food shortage. Fetal and early childhood malnutrition has been shown to increase the risk of obesity in adulthood (Black et al. 2013; Oken and Gillman 2003); therefore, nutritional status in early life may diminish the association of BMI-associated SNPs with BMI in the elderly Japanese.

The present study has several limitations. First, the sample size was relatively small, which might have led to a type 2 error. Second, although current body weight is influenced by dietary intake and physical activity during the several preceding months, we cross-sectionally examined the association of these values. Prospective studies will provide the more accurate relationship of genetic factors, dietary macronutrient intake, and physical activity with body fatness in elderly individuals. Third, our study included only male subjects. Several twin studies reported that the heritability of BMI differs by sex to a certain