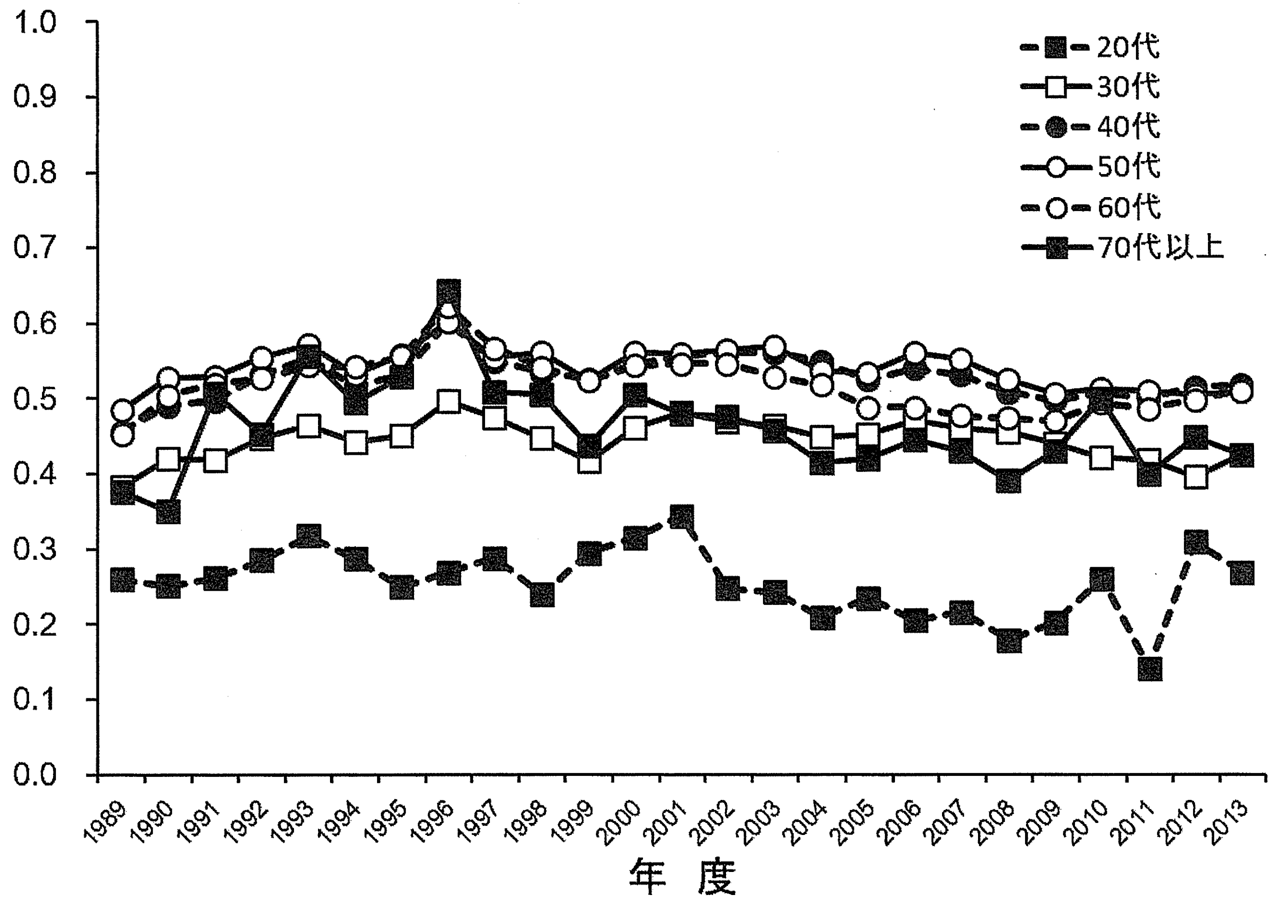

図 3. 男性の年齢群別の脂質異常症有病率推移(1989 年～2013 年)

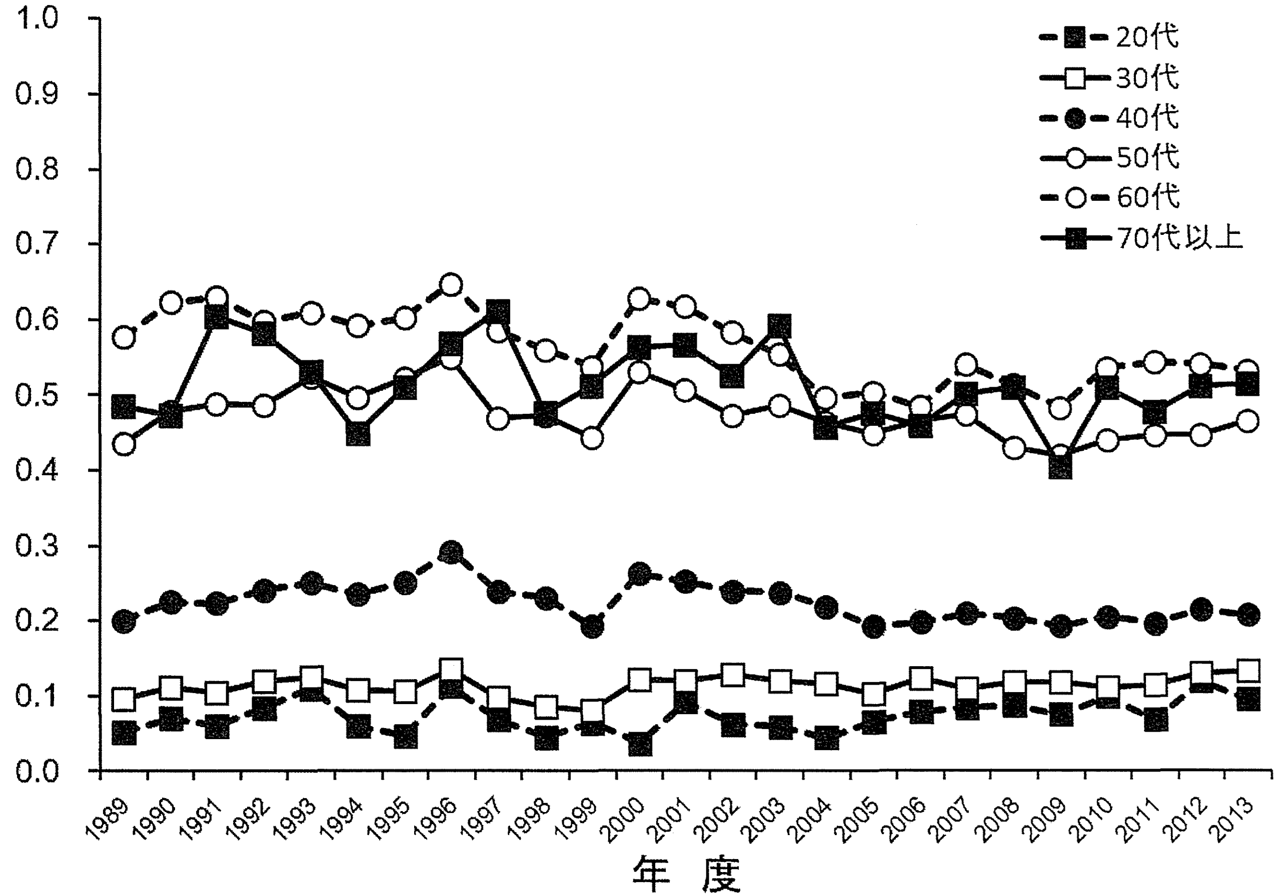

図 4. 女性の年齢群別の脂質異常症有病率推移(1989 年～2013 年)

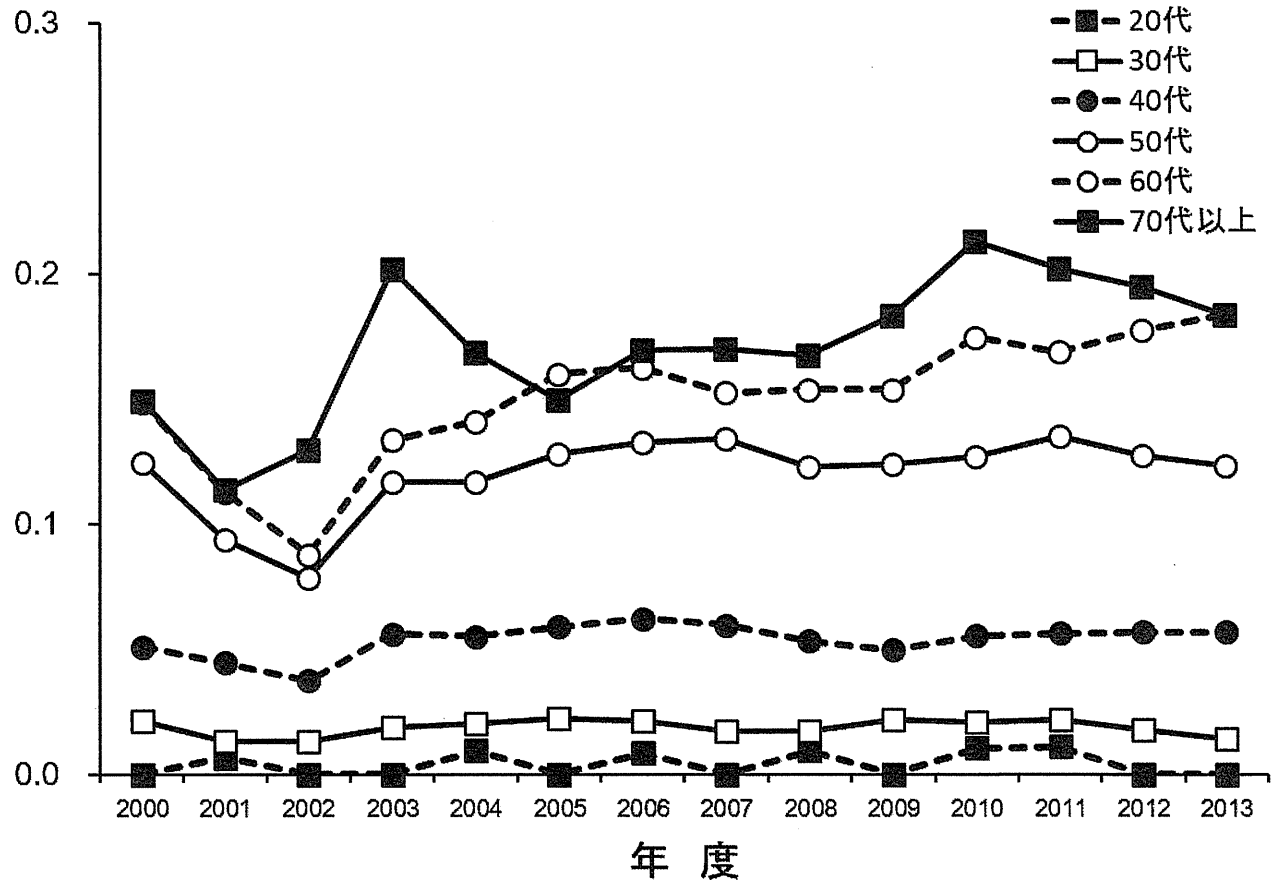

図 5. 男性の年齢群別の糖尿病有病率推移(2000 年～2013 年)

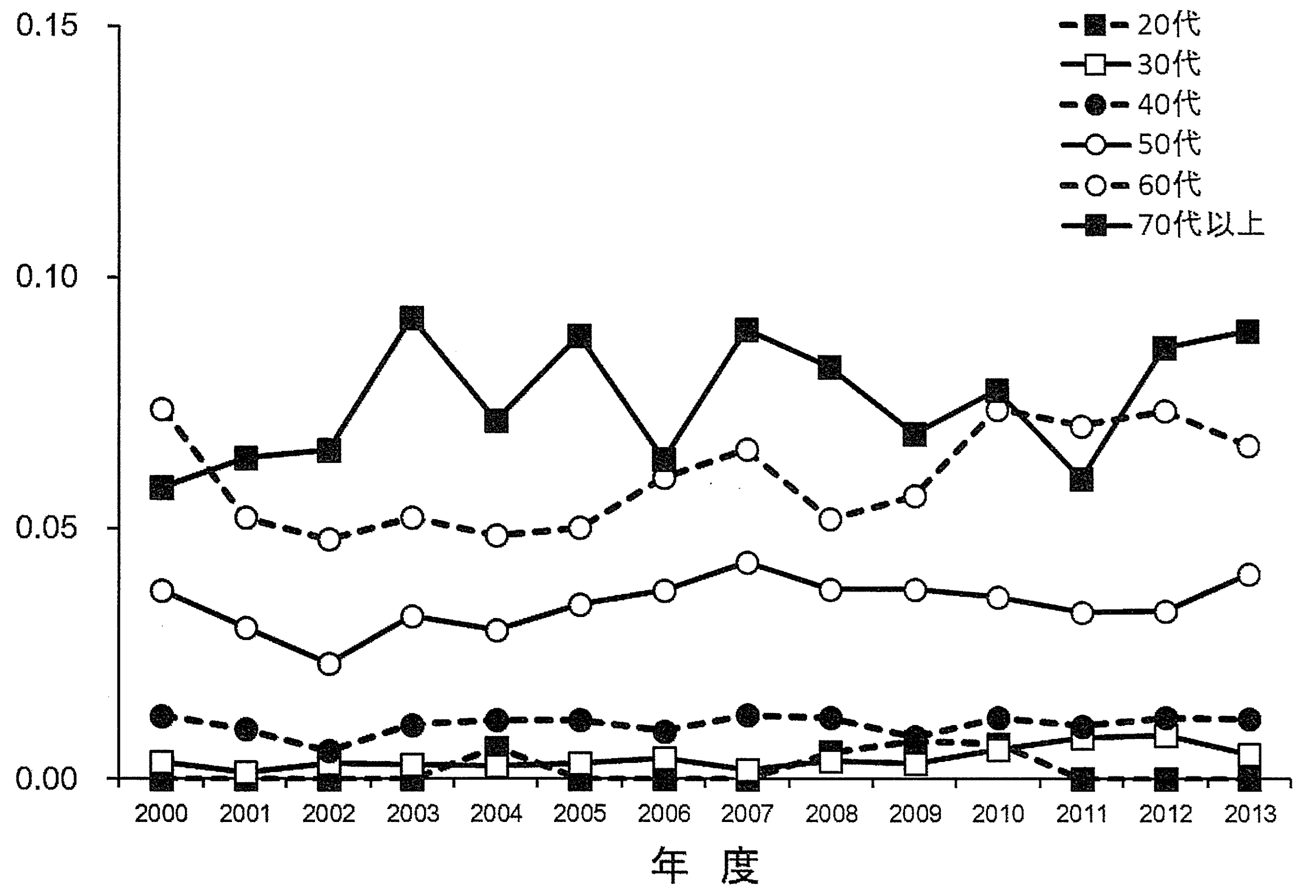

図 6. 女性の年齢群別の糖尿病有病率推移(2000 年～2013 年)

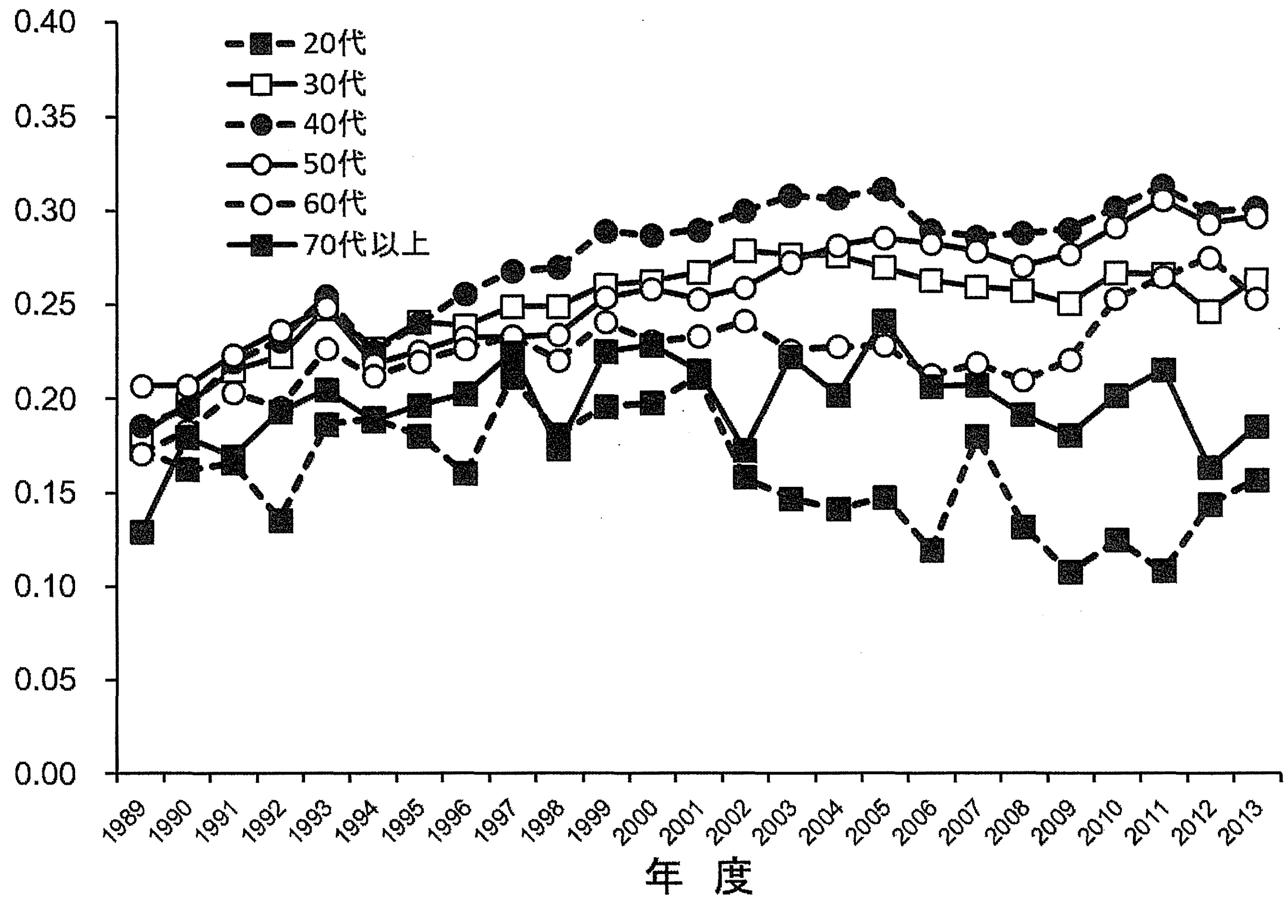

図 7. 男性の年齢群別の肥満有病率推移(1989 年～2013 年)

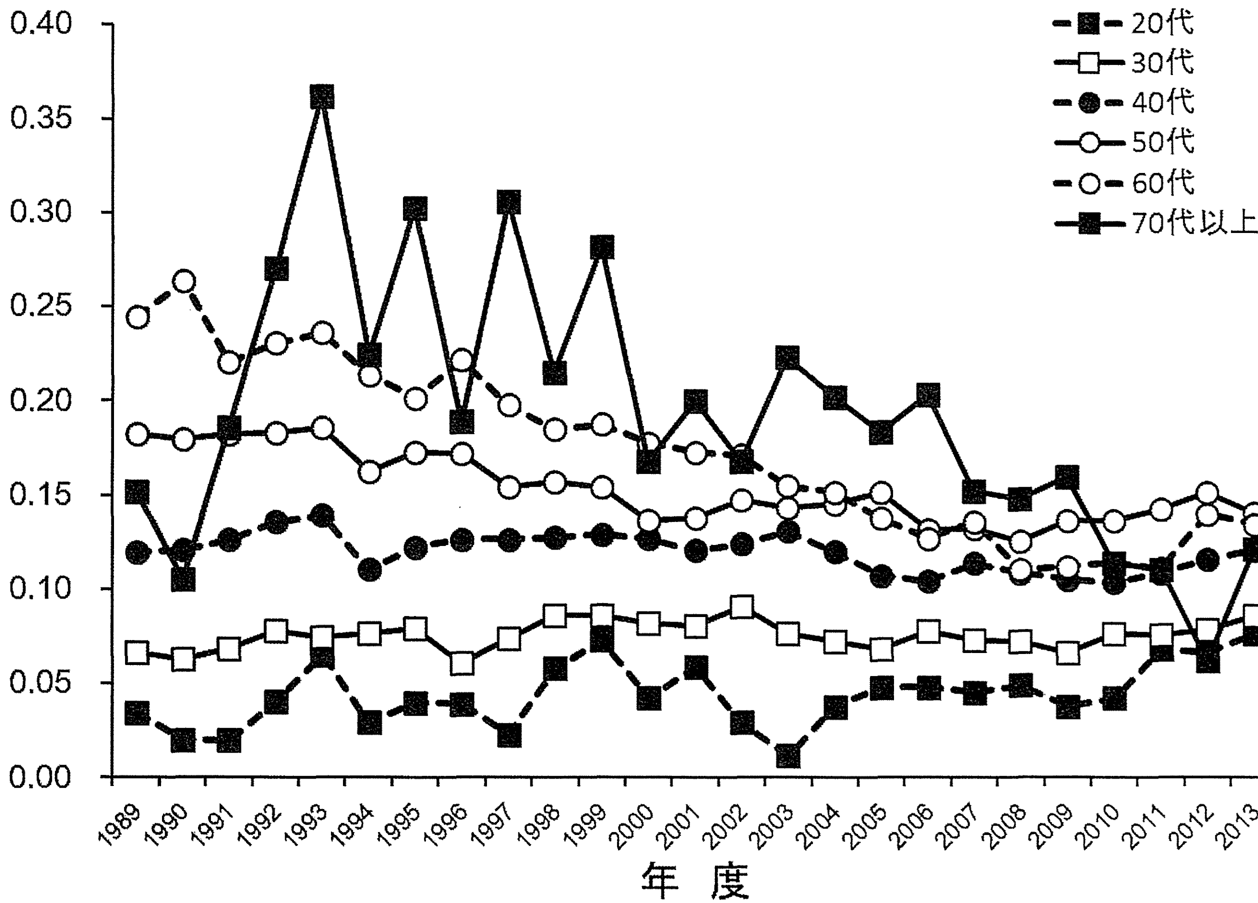

図 8. 女性の年齢群別の肥満有病率推移(1989 年～2013 年)

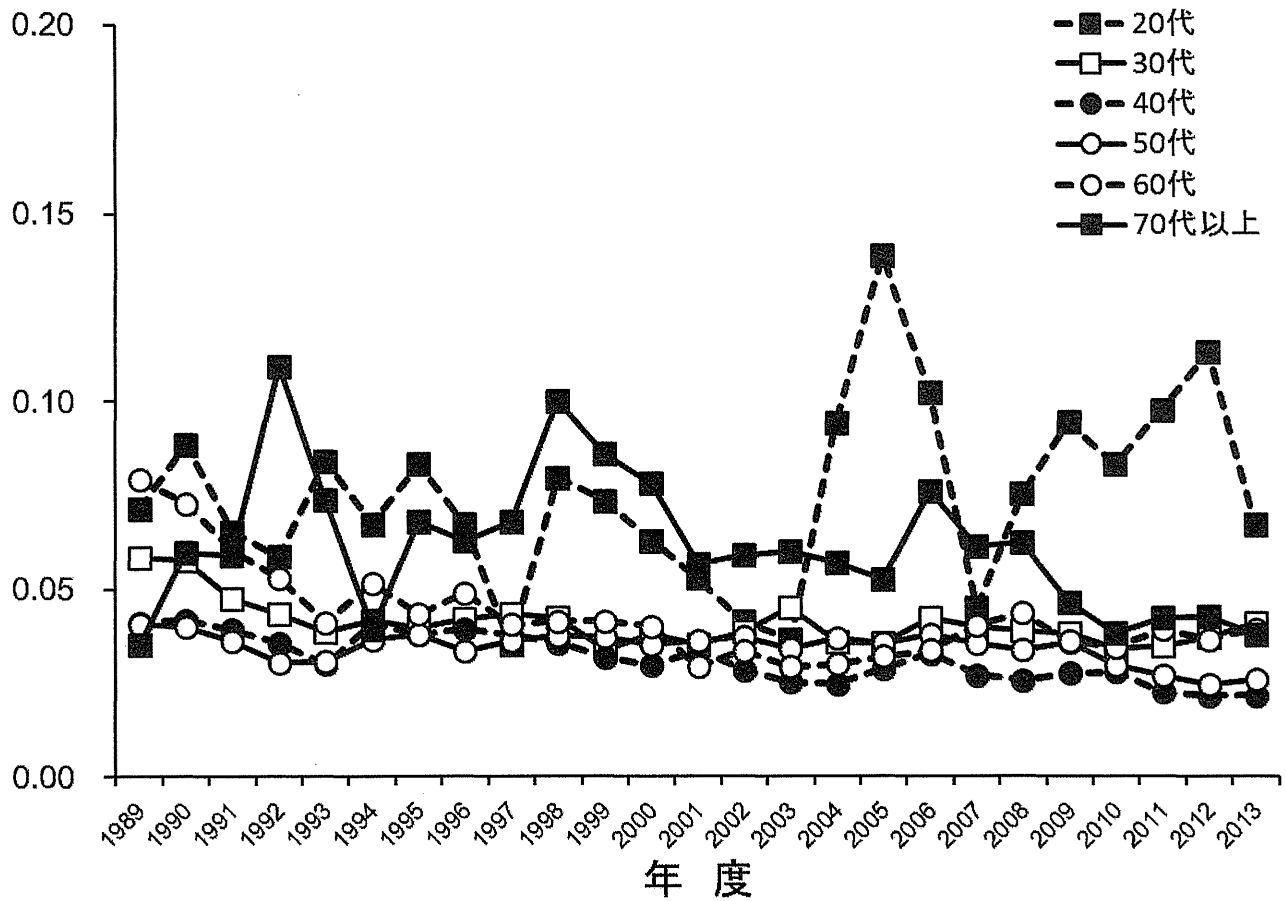

図 9. 男性の年齢群別の痩せ有病率推移（1989 年～2013 年）

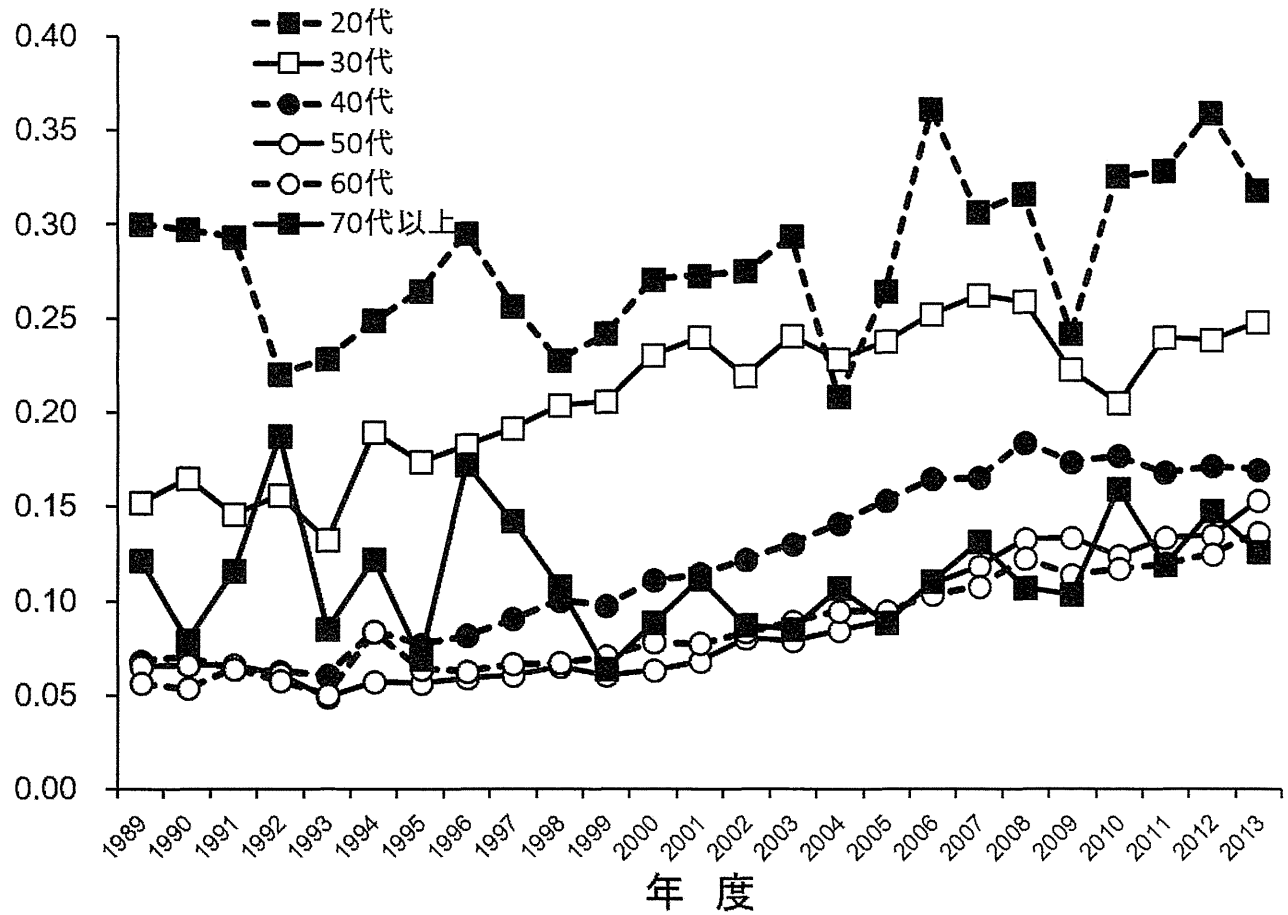

図 10. 女性の年齢群別の痩せ有病率推移(1989 年～2013 年)

Ⅲ. 研究成果の刊行に関する一覧表

雑誌

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Ⅳ. 研究成果の
刊行物・別刷

Geriatrics Gerontology Medline Indexed

Geriatr Gerontol Int 2014; **14 (Suppl. 1):** *85–92*

ORIGINAL ARTICLE

Age-related changes in skeletal muscle mass among community-dwelling Japanese: A 12-year longitudinal study

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Aim: The present study aimed to evaluate age-related changes in skeletal muscle mass among community-dwelling middle-aged and elderly Japanese.

Methods: This 12-year longitudinal study of a community-dwelling population in Japan included 15 948 examinations of 1962 men and 1990 women. We assessed appendicular muscle mass (AMM) using dual X-ray absorptiometry and calculated the skeletal muscle index (SMI) using the AMM divided by height squared (kg/m^2). Low muscle mass was defined as muscle mass minus two standard deviations below the mean for young healthy adults. Leg extension power (watts) was measured as an index of muscle function. Longitudinal data of skeletal muscle mass were analyzed using a general linear mixed-effect model.

Results: The prevalence of low muscle mass at the first wave of examinations was 27.1% in men and 16.4% in women. Longitudinal analysis showed that skeletal muscle mass decreased with aging during the 12-year study period except in middle-aged men, and to a greater extent in elderly men (*P* for trend, <0.001). Skeletal muscle mass decreased slightly, but significantly, in women. Although a cross-sectional analysis showed that SMI did not differ with age in women, leg extension power per leg muscle mass and grip strength per arm muscle mass as indices of muscle quality were significantly lower in older women (*P* for trend, <0.001 for both).

Conclusion: Age-related decreases in muscle mass were trivial, especially in women, but the quality of muscle decreased with aging in both sexes. **Geriatr Gerontol Int 2014; 14 (Suppl. 1): 85–92.**

Keywords: aging, epidemiology, longitudinal study, sarcopenia, skeletal muscle.

Introduction

Aging is associated with a progressive loss of neuromuscular function that often leads to progressive disability and loss of independence along with a reduced quality of life among the elderly.[1–6] The loss of skeletal muscle mass and strength with biological and pathological aging is now commonly described as sarcopenia.[1] This decline of skeletal muscle is thought to be inevitable even among healthy older adults. The European Working Group on Sarcopenia in Older People (EWGSOP) assumed that muscle loss is a required component for a diagnosis of sarcopenia, as well as low muscle strength and/or low physical performance.[6]

However, the rate at which community-dwelling populations lose skeletal muscle mass with aging is unclear, because accurate assessments of muscle mass can be challenging. Skeletal muscle mass can be determined by anthropometric measurements, bioelectrical impedance analysis and dual X-ray absorptiometry (DXA),[7,8] and DXA is the most effective method recommended for clinical practice.[7] However, DXA is usually impractical for epidemiological surveys, because it is costly and it involves exposure to radiation, although minimal.

The definition of low muscle mass (sarcopenia by muscle mass) proposed by Baumgartner in the Population of New Mexico Elder Health Survey has been widely applied.[9] This definition uses the ratio between appendicular skeletal muscle mass (ASM) of the upper and lower limbs (kg) and height squared (m^2; ASM/

Accepted for publication 22 November 2013.

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doi: 10.1111/ggi.12219

height^2), which is known as the skeletal muscle mass index (SMI). Thus, low muscle mass is defined as SMI ≥2 standard deviations below the normal means for a reference group aged 18–40 years determined using DXA. Several cross-sectional studies have investigated the prevalence of low muscle mass using the same definition.[6,10–18] However, the prevalence of low muscle mass has not been investigated in a longitudinal study capable of demonstrating actual changes in skeletal muscle mass with aging by repeated DXA measurements in a community-dwelling population.

The present study evaluated age-related changes in skeletal muscle mass among middle-aged and elderly Japanese men and women. Muscle mass was measured biennially up to seven times by DXA over a period of 12 years to explore actual changes in skeletal muscle mass with aging.

Methods

Participants

The study participants were derived from the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA), which involves population-based biennial examinations of a dynamic cohort of approximately 2300 individuals.[19] The participants in the NILS-LSA were community-dwelling men and women aged 40–79 years at the time of the first wave of assessments who were randomly selected from resident registrations, and stratified by sex and decade of age. Age- and sex-matched random samples of the same number of dropouts were recruited, except for those aged >79 years. New male and female participants aged 40 years were also recruited annually. The NILS-LSA is a comprehensive and interdisciplinary observational study of age-related changes that includes various gerontological and geriatric assessments of medical status, blood chemistry, body composition, anthropometry, nutritional status, psychological status, physical function, and physical activity. The first wave of NILS-LSA assessments started in November 1997. The participants were assessed approximately every 2 years until the seventh wave of examinations. We excluded those with incomplete DXA information about muscle mass. The first wave examination included 1090 men and 1081 women, and the mean number of repeat visits and length of follow up ± standard deviation (SD) were 4.04 ± 2.25 and 6.56 ± 2.25 years, respectively. A total of 1962 men and 1990 women participated in the study that comprised 15 948 assessments (including repeats). We derived data from community dwellers aged 40–91 years who participated in the NILS-LSA between November 1997 (first wave) and July 2012 (seventh wave).

The Ethics Committee of the National Center for Geriatrics and Gerontology approved the study in which all included individuals provided written informed consent to participate.

Measurement of muscle mass

Appendicular muscle mass (AMM; kg) was assessed using a QDR-4500 DXA (Hologic, Bedford, MA, USA). The AMM represents appendicular fat-free mass minus bone mineral content, and it is assumed to be an index of the amount of skeletal muscle mass.

We evaluated the SMI calculated as AMM divided by height squared (kg/m^2).[5] Low muscle mass was defined as muscle mass minus two SD below the mean for young healthy adults.[9] We set the cut-off as SMI <6.87 and <5.46 kg/m^2 for Japanese men and women, respectively, as described by Sanada *et al.*, who also measured appendicular muscle mass using the DXA apparatus as aforementioned.[15]

Other parameters

Height and weight were measured using a digital scale. Body mass index (kg/m^2) was calculated as weight divided by height squared. Medical history was assessed using questionnaires, and responses were confirmed by a physician at the time of medical assessments. Smoking habit, years of education and annual income were also assessed using a questionnaire. Trained interviewers applied a questionnaire to analyze the frequency and intensity of exercise (metabolic equivalents [MET]) to determine how free time had been spent over the past 12 months.[20] The means per day for physical activity (metabolic equivalents; MET × h/day) during leisure time were calculated. Nutritional intake was assessed using 3-day diet records.[21] Foods were weighed separately on a scale before cooking or portion sizes were estimated. Participants photographed meals before and after eating using disposable cameras. Registered dietitians used the photographs to complete missing data and telephoned participants to resolve discrepancies or obtain further information when necessary. The average of over 119 nutrients consumed over 3-day periods was calculated. The means per day for total energy intake (kcal/day) were calculated from the 3-day dietary records. Leg extension power was measured using the T.K.K.4236 adjustable seat and foot plate (Takei, Niigata, Japan). The maximum values of eight tests were included in analyses. Grip strength was also measured using the T.K.K.4301 grip dynamometer (Takei). The maximum values of two tests using the dominant hand were included in analyses.

Statistical analysis

Data were statistically analyzed using R version 3.0.1 (http://www.r-project.org/). $P < 0.05$ was considered significant. Differences in continuous and class variables between men and women were assessed using *t*-tests and χ^2-tests, respectively.

Trends in the skeletal muscle index, leg extension power/leg skeletal muscle mass, and grip strength/arm skeletal muscle mass in men and women according to age decade at the first wave examination were assessed using a general linear model.

Longitudinal data of skeletal muscle mass were analyzed using the general linear mixed-effect model, which takes into account the dependence of repeated observations within participants, which is an important feature of longitudinal analyses.[22,23] An additional advantage of the general linear mixed-effect model is that participants are included regardless of missing values. Thus, participants who were lost to follow up after early wave assessments or those who were assessed in later waves were also included in the analyses. General linear mixed-effect (lme) models were fitted using the lme function in the nlme package of R version 3.1–111. The lme function fits general linear mixed-effect models. The intragroup correlation structure was specified as a compound symmetry structure that corresponded to a constant correlation.

The effects of birth year on the rate of change in appendicular skeletal muscle mass over time were evaluated using general LME models. We determined fixed effects, such as average effects for birth cohorts, and random effects, such as individual deviations from the fixed effects to model changes in the mass of individual muscles. Birth year was categorized as 1920s or before, the 1930s, 1940s and 1950s, and thereafter. Time is expressed as years from time 0 defined as 1 October 2005, to approximately the midpoint between the first and the last waves of assessments to reduce the influence of collinearity. Appendicular skeletal muscle mass was estimated from the fixed effects of time, birth cohort, time × birth cohort interaction, and random effects of the intercept (individual differences in basic values for muscle mass) and slope (individual changes in muscle mass over time). Smoking, alcohol consumption, years of education, annual income and comorbidities (hypertension, heart disease, dyslipidemia, diabetes mellitus and stroke) were controlled in the model. Data from 1869 men (7297 assessments) and 1868 women (7095 assessments) with no missing values in covariates were analyzed in the linear mixed effect model.

Results

Table 1 shows the characteristics of the participants by sex at the first wave of assessments. Men were significantly taller and heavier than women (each, $P < 0.001$), but the body mass index was essentially the same. Among 1090 men and 1081 women, 295 (27.1%) and 177 (16.4%) were diagnosed with low muscle mass at the first wave of assessments, respectively. The ratio (%) was significantly higher in men than in women ($P < 0.001$ for both). AMM and SMI were also significantly higher in men than in women ($P < 0.001$ for both), with no difference in age between men and women. More men smoked and consumed alcohol than women ($P < 0.001$ for both). Men spent more years being educated than women, and had higher annual incomes ($P < 0.001$ for both). Grip strength and leg extension power were significantly stronger in men than in women ($P < 0.001$ for both). Men were more likely to have a history of diabetes and stroke than women ($P = 0.004$ and 0.007, respectively), but women were more likely to have a history of dyslipidemia than men ($P < 0.001$), although hypertension and heart disease did not differ between the sexes. Men consumed significantly more total energy, and participated in leisure-time physical activities more frequently and at a greater intensity than women ($P < 0.001$ for both).

Figure 1 shows SMI by age decade in men and women. The SMI was lower in older than in younger men (P for trend, < 0.001), but did not differ by age in women (P for trend, not significant). Leg extension power (watts) divided by leg skeletal muscle mass (kg) was used as an index of leg muscle performance. Leg extension power per leg skeletal muscle mass (watts/kg) by age decade was significantly lower in older men and women (P for trend, <0.001 for both; Figure 2a). Handgrip strength (kg) divided by arm skeletal muscle mass (kg) was used as an index of hand muscle performance. Handgrip strength per arm skeletal muscle mass (kg/kg) by age decade was also significantly lower in older men and women (P for trend, <0.001 for both; Figure 2b).

Figure 3 shows estimated 12-year changes in SMI by birth cohort between 1998 and 2010 in 1869 men (7297 assessments) and 1868 women (7095 assessments). Changes in SMI by birth cohort were estimated using the general linear mixed-effect model controlled for smoking, alcohol consumption, years of education, annual income and comorbidities (hypertension, heart disease, dyslipidemia, diabetes mellitus and stroke). The main effects of time ($P = 0.03$), birth cohort ($P < 0.001$), and interaction between time and birth ($P < 0.001$) in men were significant. However, only the main effects of time were significant in women ($P < 0.001$).

The estimated SMI values in men were larger in younger birth cohorts in 1998 and 2010 ($P < 0.001$ for both), and the trend in slope by birth cohort was also significant. The estimated SMI significantly decreased in the 1920s ($P < 0.001$), 1930s ($P < 0.001$) and 1940s ($P = 0.005$) birth cohorts. However, the estimated SMI slightly, but significantly, increased in the 1950s ($P < 0.001$) birth cohort. The estimated SMI values in women did not increase by birth cohort in 1998 and

Table 1 Characteristics of study participants by sex at first wave of examinations

Variable	Men (n = 1090)	Women (n = 1081)	t-test/χ^2 test	
Age (years)	59.3 ± 11.0	59.3 ± 10.9	t (2169) = 0.07	NS
Height (cm)	164.5 ± 6.4	151.3 ± 6.1	t (2169) = 49.45	***
Weight (kg)	62.1 ± 9.1	52.4 ± 8.2	t (2169) = 26.02	***
BMI (kg/m²)	22.9 ± 2.8	22.9 ± 3.3	t (2169) = 0.09	NS
Smoking				
Never smoker, n (%)	237 (21.7%)	968 (89.7%)	χ^2 (2) = 1023.51	
Ex-smoker, n (%)	440 (40.4%)	31 (2.9%)		***
Current smoker, n (%)	413 (37.9%)	80 (7.4%)		
Alcohol consumption (ethanol mL/day)	16.0 ± 19.3	2.6 ± 5.6	t (2073) = 21.54	***
Education (year)	12.1 ± 2.5	11.4 ± 2.1	t (2161) = 7.38	***
Annual income (yen)				
<4 500 000	267 (24.8%)	332 (32.9%)	χ^2 (2) = 18.8	
≥4 000 000 and <7 5000 000	379 (35.2%)	292 (28.9%)		***
≥7 5000 000	432 (40.1%)	385 (38.2%)		
Grip strength (kg)	41.6 ± 7.9	25.0 ± 5.2	t (2146) = 57.49	***
Leg extension power (watts)	533.6 ± 184.4	301.4 ± 106.8	t (2058) = 34.80	***
Medical history				
Hypertension, n (%)	191 (17.6%)	210 (19.5%)	χ^2 (1) = 1.33	NS
Heart Disease, n (%)	71 (6.5%)	65 (6.0%)	χ^2 (1) = 0.23	NS
Dyslipidemia, n (%)	55 (5.1%)	98 (9.1%)	χ^2 (1) = 13.40	***
Diabetes mellitus, n (%)	71 (6.5%)	41 (3.8%)	χ^2 (1) = 8.24	**
Stroke, n (%)	23 (2.1%)	8 (0.7%)	χ^2 (1) = 7.27	*
AMM (kg)	20.0 ± 2.8	14.0 ± 2.0	t (2169) = 57.76	***
SMI (kg/m²)	7.36 ± 0.80	6.11 ± 0.70	t (2169) = 38.82	***
Prevalence of low muscle mass, n (%)	295 (27.1%)	177 (16.4%)	χ^2 (1) = 36.46	***
Total energy intake (kcal/day)	2323.7 ± 420.5	1894.3 ± 322.2	t (2073) = 26.11	***
Leisure-time PA (MET × min / year / 1000)	47.6 ± 59.9	30.8 ± 43.3	t (2135) = 7.44	***

Data are shown as means ± standard deviation. *P < 0.05, **P < 0.01, ***P < 0.001. Final sample comprised 2171 participants at first wave assessment. Missing data: Smoking, n = 2; Alcohol (ethanol) consumption, n = 96; Education, n = 8; Annual income, n = 101; Grip strength, n = 23; Leg extension power, n = 111; Hypertension, n = 7; Heart disease, n = 7; Dyslipidemia, n = 14; Diabetes mellitus, n = 11; stroke, n = 10; Total energy intake, n = 96; PA, n = 34. Cut-offs for low muscle mass in men and women: SMI <6.87 and 5.46 kg/m², respectively. AMM, appendicular muscle mass; BMI, body mass index; NS, not significant; PA, physical activity during leisure time; SMI, skeletal muscle index calculated by appendicular muscle mass divided by height squared.

2010, and slightly but significantly decreased in all birth cohorts. No trends in the slopes by birth cohort were evident (P for trend, not significant).

Table 2 shows the fixed effects of birth cohorts and of interactions between time and birth cohorts in the model without the intercept and the main effect of time in men and women. In this model, each fixed effect of birth cohort was an intercept of the birth cohort; that is, the estimated SMI at time 0 (1 October 2005) of each birth cohort, and the fixed effects of the interaction between time and birth cohort were slopes (annual changes) of the birth cohorts.

Discussion

Older persons commonly lose bone and skeletal muscle mass, and gain a relative amount of fat mass. Sarcopenia is characterized by progressive and generalized loss of skeletal muscle mass and strength, and it increases the risk of disability and a poor quality of life.[1,2,24]

Primary sarcopenia is caused by normal aging, but the manner and speed of skeletal muscle mass decrease in community-dwelling populations remain unclear. Here, we confirmed a significant decrease in skeletal muscle mass with aging except among middle-aged men. The prevalence of low muscle mass in the present study was 27.1% in men and 16.6% in women. However, the prevalence varies from 8% to 40% of people aged >60 years depending on the study sample, age, definition and assessment tool.[11] Values obtained using DXA comprise the most accepted method of quantifying muscle mass in research and clinical practice.[7] The cut-off for low muscle mass ≥2 SD below the young adult mean (YAM) derived from individuals aged between 18

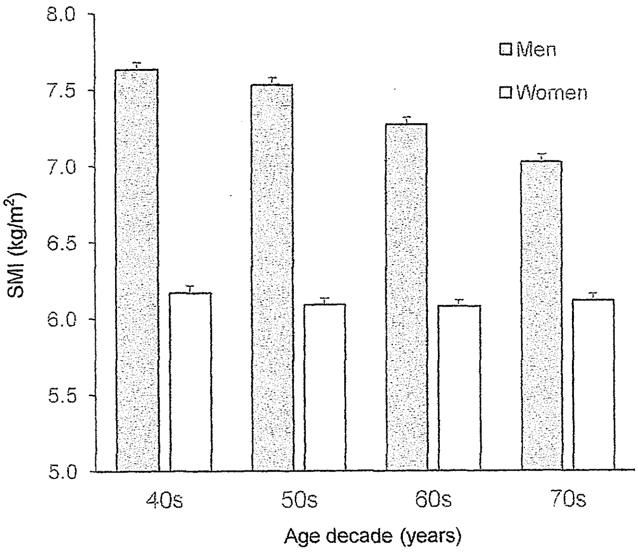

Figure 1 Skeletal muscle index (SMI) of men and women according to age decade (mean ± standard error). SMI is lower in older than in younger men (*P* for trend, <0.001), but does not differ according to age among women (*P* for trend, not significant).

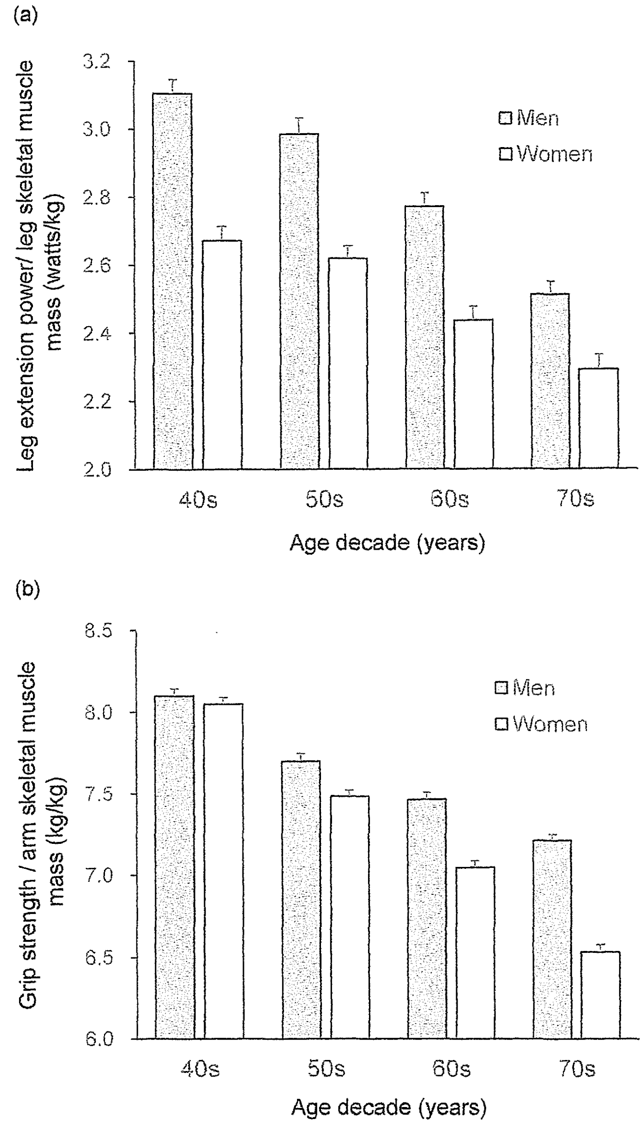

Figure 2 (a) Leg extension power/leg skeletal muscle mass and (b) grip strength/arm muscle mass according to sex and age (mean ± standard error). Both values are significantly lower in older men and women (*P* for trend, <0.001 for both).

and 80 years, but obtaining reference values from relevant young, healthy, sex and ethnicity-matched populations can be challenging. Thus, some studies have used the lowest third of fat-free mass (FFM) to define low muscle mass.[16,25]

The New Mexico Elder Health Survey defined cut-offs for SMI as 7.26 and 5.45 kg/m^2 for men and women, respectively, based on ≥2 SD below the YAM.[9] They found that the prevalence of low muscle mass in persons aged <70 years increased from 13–24% to >50% in those aged >80 years. Although some cross-sectional studies have studied the prevalence of low muscle mass according to the same definition, the prevalence greatly differs depending on the cohort. The prevalence was 35.3% in men and 34.7% in women aged between 20 and 84 years in a Thai population,[10] and 8.9% and 10.9% in women aged 76–80 years and 86–95 years in the Epidemiologie de l'Osteoporose cohort, which was an observational, prospective and multicenter cohort study of French community-dwelling women aged ≥75 years.[11,12] The prevalence of low muscle mass had been reported to be 64.0% and 95.0% for female and male inpatients with hip fractures, respectively,[14] 6.7% and 6.3% among healthy male and female Japanese volunteers aged 70–85 years,[15] and 10.4% among female patients in an orthopedic outpatient clinic with normal lumbar spine bone mineral density.[17] A cross-sectional study of a Chinese population found the prevalence of low muscle mass of 13.2% for men and 4.8% for women aged ≥70 years.[18] The Korean National Health and Nutrition Examination Survey identified a 9.9% prevalence of low muscle mass among men age ≥60 years.[13]

Cooper *et al.* stated that assessments of sarcopenia should not depend only on muscle mass, but on a combination of measures of muscle mass and physical performance.[8] EWGSOP suggested an algorithm for sarcopenia case findings among older individuals based on measurements of gait speed, grip strength and muscle mass.[6] We found a rather small decrease in skeletal muscle mass; however, the muscle performance was greatly reduced, especially in women, which could cause frailty and disrupted daily activities among elderly women. The prevalence of sarcopenia was also determined according to the EWGSOP algorithm