資料 3.「その他の生活習慣介入による代謝異常の改善」の Cochrane Data Base での検索式と抽出文献数

番号	検索式	文献数
#1	NONOBES* or NON next OBES* or WITHOUT next OBES*	1,093
#2	(NORMAL* or ADEQUATE*) near/3 (WEIGHT* or BMI or (BODY next MASS) or CIRCUMFER* or (BODY next FAT*))	2,030
#3	(WAIST* or WC) near/3 (LESS or BELOW or LOWER or UNDER or LTOREQ) near/3 (85CM or 85 or 90CM or 90 or 850 or 900 or 850MM or 900MM)	0
#4	(BMI or (BODY near/1 MASS)) near/3 (LESS or BELOW or LOWER or UNDER or LTOREQ) near/3 (25 or 25KG*)	66
#5	MONW or MANW or MUHNW or (MUH next NW)	2
#6	MeSH descriptor: [Dyslipidemias] explode all trees	5,036
#7	MeSH descriptor: [Metabolic Diseases] this term only	127
#8	MeSH descriptor: [Lipid Metabolism Disorders] this term only	8
#9	MeSH descriptor: [Glucose Metabolism Disorders] explode all trees	18,053
#10	MeSH descriptor: [Hypertension] explode all trees	14,303
#11	MeSH descriptor: [Metabolic Syndrome X] explode all trees	952
#12	*METABOLIC* near/1 (OBES* or DISEASE* or SYNDROME* or SYMPTOM*) or (INSULIN* next RESISTAN*)	9,332
#13	*METABOLIC* near/3 (UNHEALTH* or (UN near/1 HEALTH*) or ABNORMAL* or DYSREGULAT* or DISTURB* or DISORDER* or ANOMAL*)	2,263
#14	HYPERGLYCEMI* or HYPERGLYCAEMI* or (GLUCOSE* near/2 (ANOMAL* or ABNORMAL* or *TOLERAN* or IMPAIR* or DISORDER* or ELEVAT* or HIGH* or INCREASE* or RISE* or RISING*)) or DIABET* or NIDDM	49,577
#15	HYPERTENS* or (BLOOD near/1 PRESSUR* near/3 (ANOMAL* or ABNORMAL* or DISORDER* or ELEVAT* or HIGH* or INCREASE* or RISE* or RISING*))	44,274
#16	HYPERLIPID* or DYSLIPID* or (LIPID* near/2 (ANOMAL* or ABNORMAL* or DISORDER* or ELEVAT* or HIGH* or INCREASE* or RISE* or RISING*)) or (LIPID* near/1 (DISEASE* or DISORDER*))	7,284
#17	HYPERTRIGLYCERID* or (TRIGLYCERID* near/2 (ANOMAL* or ABNORMAL* or DISORDER* or ELEVAT* or HIGH* or INCREASE* or RISE* or RISING*))	2,753
#18	HYPERCHOL* or CHOLESTEROL* near/2 (ANOMAL* or ABNORMAL* or ANOMAL* or ABNORMAL* or DISORDER* or ELEVAT* or INCREASE* or RISE* or RISING*)	6,841
#19	TWO near/2 MORE near/2 METABOLIC* near/2 (COMPONENT* or RISK* or FACTOR*)	1
#20	MeSH descriptor: [Blood Pressure] explode all trees	23,536
#21	MeSH descriptor: [Cholesterol] explode all trees	8,513
#22	MeSH descriptor: [Triglycerides] this term only	5,112
#23	MeSH descriptor: [Blood Glucose] explode all trees	11,505
#24	MeSH descriptor: [Lipids] this term only	5,252

#25	MeSH descriptor: [Hemoglobin A, Glycosylated] explode all trees	3,822
#26	(SERUM or BLOOD or PLASMA* or FASTING* or CASUAL*) near/3 GLUCOSE*	23,000
#27	HBA1C or (GLYCOSYL* or GLYCAT*) near/2 (HEMOGLOBIN* or HAEMOGLOBIN*) or HB near/1 (A1 or A1C) or (*HEMOGLOBIN* or *HAEMOGLOBIN*) near/1 (A or A1 or A1c) or HOMA near/1 (R or IR or BETA) or HOMEOSTA* near/1 MODEL*	12,098
#28	BLOOD near/1 PRESSUR* or CHOLESTEROL* or TRIGLYCERID* or LDL or HDL or NONHDL	75,611
#29	(#1 or #2 or #3 or #4 or #5) and (#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28) Publication Year from 1995 to 2015	1,206
#30	obesit*:ti and (#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28) Publication Year from 1995 to 2015	968
#31	MeSH descriptor: [Pregnant Women] explode all trees	103
#32	MeSH descriptor: [Pregnancy] explode all trees	5,924
#33	MeSH descriptor: [Pregnancy Complications] explode all trees	8,061
#34	(PREGNAN* or MATERN* or gravid* or childbear* or prenatal*):ti	11,328
#35	MeSH descriptor: [Pediatrics] explode all trees	567
#36	MeSH descriptor: [Child] explode all trees	240
#37	MeSH descriptor: [Infant] explode all trees	13,476
#38	MeSH descriptor: [Pediatric Obesity] explode all trees	48
#39	(child* or pediatr* or paediatr* or INFANT* or NEWBORN* or BABY or BABIES or NEONAT*):ti	65,511
#40	MeSH descriptor: [Adult] explode all trees	1,838
#41	(adult* or elder* or senior* or middle next age* or aged):ti	33,528
#42	(#29 not (#31 or #32 or #33 or #34 ot #35 or #36 or #37 or #38 or #39)) or (#29 and (#40 or #41))	1,073
#43	(#30 not (#31 or #32 or #33 or #34 ot #35 or #36 or #37 or #38 or #39)) or (#29 and (#40 or #41))	961
#44	MeSH descriptor: [Life Style] explode all trees	2,921
#45	MeSH descriptor: [Health Behavior] this term only	2,601
#46	MeSH descriptor: [Risk Reduction Behavior] this term only	1,183
#47	(LIFESTYL* or LIFE near/1 STYL*):ti	1,749
#48	#44 or #45 or #46 or #47	6,885
#49	MeSH descriptor: [Drinking Behavior] explode all trees	2,648
#50	MeSH descriptor: [Temperance] explode all trees	270
#51	MeSH descriptor: [Drinking] explode all trees	438
#52	MeSH descriptor: [Alcoholic Beverages] explode all trees	403

#53	(DRINK* or (ALCOHOL* not ALCoHOL* near/1 (FATTY* or LIVER* or STEATOHEPA*)) or TEMPERAN*):ti	2,068
#54	#49 or #50 or #51 or #52 or #53	4,787
#55	MeSH descriptor: [Tobacco Use] explode all trees	4,960
#56	MeSH descriptor: [Tobacco Use Cessation] explode all trees	3,004
#57	(TOBACCO or SMOKING* or SMOKE* or cigaret*):ti	9,485
#58	#55 or #56 or #57	11,537
#59	MeSH descriptor: [Sleep] explode all trees	4,154
#60	((SLEEP* not SLEEP near/1 APNEA*) or SLEEP near/1 (DURAT* or QUALITY* or PATTERN*)):ti	535
#61	#59 or #60	4,511
#62	#42 and (#48 or #54 or #58 or #61)	63
#63	#43 and (#48 or #54 or #58 or #61)	88
#64	#62 or #63	138

Ⅲ. 研究成果の刊行に関する一覧表

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Ⅳ. 研究成果の刊行物・別刷

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ORIGINAL ARTICLE

Incidence of disability and its associated factors in Japanese men and women: the Longitudinal Cohorts of Motor System Organ (LOCOMO) study

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Abstract We investigated the incidence of disability and its risk factors in older Japanese adults to establish an evidence-based disability prevention strategy for this population. For this purpose, we used data from the Longitudinal Cohorts of Motor System Organ (LOCOMO) study, initiated in 2008 to integrate information from cohorts in nine communities across Japan: Tokyo (two regions), Wakayama (two regions), Hiroshima, Niigata, Mie, Akita, and Gunma prefectures. We examined the annual occurrence of disability from 8,454 individuals (2,705 men and 5,749 women) aged ≥65 years. The estimated incidence of disability was 3.58/100 person-years (p-y) (men: 3.17/100 p-y; women: 3.78/100 p-y). To determine factors associated with disability, Cox's proportional hazard model was used, with the occurrence of disability as an objective variable and age (+1 year), gender (vs. women), body build (0: normal/overweight range, BMI 18.5–27.5 kg/m^2; 1: emaciation, BMI <18.5 kg/m^2; 2: obesity, BMI >27.5 kg/m^2), and regional differences (0: rural areas including Wakayama, Niigata, Mie, Akita, and Gunma vs. 1: urban areas including Tokyo and Hiroshima) as explanatory variables. Age, body build, and regional difference significantly influenced the occurrence of disability (age, +1 year: hazard ratio 1.13, 95 % confidence interval 1.12–1.15, $p < 0.001$; body build, vs. emaciation: 1.24, 1.01–1.53, $p = 0.041$; body build, vs. obesity: 1.36, 1.08–1.71, $p = 0.009$; residence, vs. living in rural areas: 1.59, 1.37–1.85, $p < 0.001$). We concluded that higher age,

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both emaciation and obesity, and living in rural areas would be risk factors for the occurrence of disability.

Keywords Nation-wide population-based cohort study · Epidemiology · Incidence · Disability · Body build

Introduction

In Japan, the proportion of the population aged 65 years or older has increased rapidly over the years. In 1950, 1985, 2005, and 2010, this proportion was 4.9, 10.3, 19.9, and 23.0 %, respectively [1]. Further, this proportion is estimated to reach 30.1 % in 2024 and 39.0 % in 2051 [2]. The rapid aging of Japanese society, unprecedented in world history, has led to an increase in the number of disabled elderly individuals requiring support or long-term care. The Japanese government initiated the national long-term care insurance system in April 2000 in adherence with the Long-Term Care Insurance Act [3]. The aim of the national long-term care insurance system was to certify the level of care needed by elderly adults and to provide suitable care services to them according to the levels of their long-term care needs. According to the recent National Livelihood Survey by the Ministry of Health, Labour and Welfare in Japan, the number of elderly individuals certified as needing care services increases annually, having reached 5 million in 2011 [4].

However, few prospective, longitudinal, and cross-national studies have been carried out to inform the development of a prevention strategy against disability. To establish evidence-based prevention strategies, it is critically important to accumulate epidemiologic evidence, including the incidence of disability, and identify its risk factors. However, few studies have attempted to estimate the incidence of the disability and its risk factors by using population-based cohorts. In addition, to identify the incidence of disability, a study should have a large number of subjects. Further, to determine regional differences in epidemiological indices, a survey of cohorts across Japan is required.

The Longitudinal Cohorts of Motor System Organ (LOCOMO) study was initiated in 2008, through a grant from Japan's Ministry of Health, Labour and Welfare, for the prevention of knee pain, back pain, bone fractures, and subsequent disability. It aimed to integrate data gathered from cohorts from 2000 onwards and follow-up surveys from 2006 onwards, using a unified questionnaire, with an ultimate goal being the prevention of musculoskeletal diseases. The present study specifically aims at using LOCOMO data, which is based on the long-term care insurance system, to investigate the occurrence of disability in order to clarify its incidence and risk factors, especially in terms of body build and regional differences.

Materials and methods

Participants were residents of nine communities located in Tokyo (two regions: Tokyo-1, principal investigators (PIs): Shigeyuki Muraki, Toru Akune, Noriko Yoshimura, Kozo Nakamura; Tokyo-2, PIs: Yoko Shimizu, Hideyo Yoshida, Takao Suzuki), Wakayama [two regions: Wakayama-1 (mountainous region) and Wakayama-2 (coastal region), PIs: Noriko Yoshimura, Munehito Yoshida], Hiroshima (PI: Saeko Fujiwara), Niigata (PI: Go Omori), Mie (PI: Akihiro Sudo), Akita (PI: Hideyo Yoshida), and Gunma (PI: Yuji Nishiwaki) prefectures [5]. Figure 1 shows the location of each cohort in Japan.

Disability in the present study was defined as 'cases requiring long-term care', as determined by the long-term care insurance system. The procedure for identifying these cases is as follows: (1) each municipality establishes a long-term care approval board consisting of clinical experts, physicians, and specialists at the Division of Health and Welfare in each municipal office; (2) The long-term care approval board investigates the insured person by using an interviewer-administered questionnaire consisting of 82 items regarding mental and physical conditions, and makes a screening judgement based on the opinion of a regular doctor; (3) 'Cases requiring long-term care' are determined according to standards for long-term care certification that are uniformly and objectively applied nationwide [6].

In order to identify the incidence of disability, data were collected from participants aged 65 years and older within the above-mentioned cohorts. In Japan, most individuals certified as 'cases requiring long-term care' are 65 years and older. Table 1 shows the number of subjects per region, as well as the data obtained within the first year of the observation. The smallest cohort consisted of 239 subjects, residing in Mie, while the largest consisted of 1,758, who resided in Gunma.

The earliest baseline data were collected in 2000 in Hiroshima, while the latest were obtained in 2008 in Tokyo-2. The cohorts were subsequently followed until 2012. Data regarding participants' deaths, changes of residence, and occurrence or non-occurrence of certified disability were gathered annually from public health centres of the participating municipalities. As an index of body build, baseline data on participants' height and weight were collected, and used to calculate body mass index (BMI, kg/m^2). Participants were classified as follows: normal or overweight (BMI = 18.5–27.5), obese (BMI >27.5), or emaciated (BMI <18.5). These cut-off points were determined according to a WHO report [7]. From 2008 onwards, follow-up data was obtained using the unified questionnaire.

All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo (nos. 1264 and 1326), the Tokyo Metropolitan Institute of Gerontology

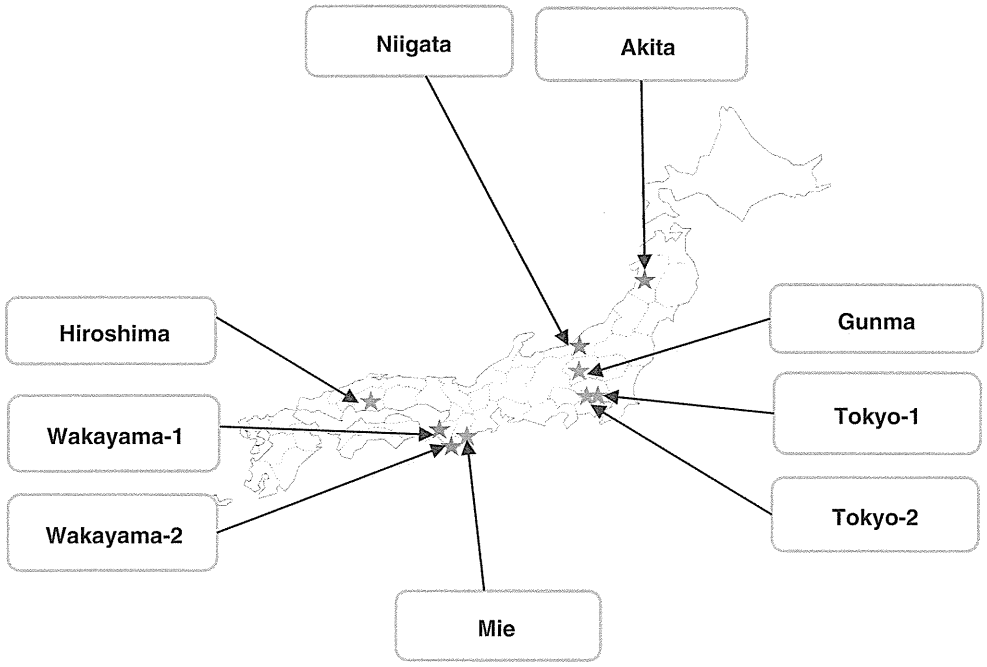

Fig. 1 Location of nine regions from which the study cohorts were selected

Table 1 Number of subjects classified by regions of each cohort

Region	Start year	Total	Men	Women
Tokyo-1	2005	1,332	461	871
Tokyo-2	2008	1,453	59	1,394
Wakayama-1 (Mountainous)	2005	610	239	371
Wakayama-2 (Coastal)	2006	357	129	228
Hiroshima	2000	1,341	351	990
Niigata	2007	805	343	462
Mie	2001	239	95	144
Akita	2006	559	223	336
Gunma	2005	1,758	805	953
Total		8,454	2,705	5,749

(no. 5), Wakayama (no. 373), the Radiation Effects Research Foundation (RP 03-89), Niigata University (no. 446), Mie University (nos. 837 and 139), Keio University (no. 16–20), and the National Center for Geriatrics and Gerontology (no. 249). Careful consideration was given to ensure the safety of the participants during all of the study procedures.

Statistical analysis

All statistical analyses were performed using STATA (STATA Corp., College Station, Texas, USA). Differences in proportions were compared using the chi-squared test. Differences in continuous variables were tested using an analysis of variance (ANOVA) with Scheffe's least significant difference test for post-hoc pairwise comparisons. To test the association between the occurrence of disability and other variables, Cox's proportional hazard regression analysis was used. Hazard ratios (HRs) were estimated using the occurrence of disability as an objective variable (0: non-occurrence, 1: occurrence) and the following explanatory variables: age (±1 year), gender (vs. female), body build (0: normal and overweight vs. 1: emaciation vs. 2: obesity), and regional differences (0: rural areas, including Wakayama-1, Wakayama-2, Niigata, Mie, Akita, and Gunma vs. 1: urban areas, including Tokyo-1, Tokyo-2, and Hiroshima). All p values and 95 % confidence intervals (CI) of two-sided analyses are presented.

Results

Table 2 shows the number of participants classified by age and gender. The majority of participants were 75–79 years old; two-thirds of the participants were women.

Selected characteristics of the study population, including age, height, weight, and BMI, are shown in Table 3. The mean values of age, height, and weight were significantly greater in women than in men ($p < 0.001$), but BMI did not significantly differ between men and women ($p = 0.479$).

The estimated incidence of disability is shown in Fig. 2. In total, the incidence of disability among individuals aged 65 years and older was 3.58/100 person-years (p-y) (p-y; men: 3.17/100 p-y; women: 3.78/100 p-y). The incidence of disability was 0.83/100 p-y, 1.70/100 p-y, 3.00/100 p-y,

Table 2 Number of subjects classified by age and gender

Age strata (years)	Total (%)	Men (%)	Women (%)
65–69	1,390 (16.4)	555 (20.5)	835 (14.5)
70–74	1,704 (20.2)	668 (24.7)	1,036 (18.0)
75–79	2,923 (34.6)	812 (30.0)	2,111 (36.7)
80–84	1,810 (21.4)	463 (17.1)	1,347 (23.4)
≥85	627 (7.4)	207 (7.7)	420 (7.3)
Total	8,454 (100.0)	2,705 (100.0)	5,749 (100.0)

Table 3 Baseline characteristics of subjects classified by age and gender

Variables	Men	Women	*p* (men vs. women)
Age (years)	75.3 (6.4)	76.5 (6.0)	<0.001
Height (cm)	160.5 (6.5)	147.7 (6.1)	<0.001
Weight (kg)	58.7 (9.1)	49.8 (8.4)	<0.001
BMI (kg/m^2)	22.7 (2.9)	22.8 (3.5)	0.479
Living in rural area (%)	84.8	58.5	<0.001

Values are represented as mean (standard deviation)

BMI body mass index

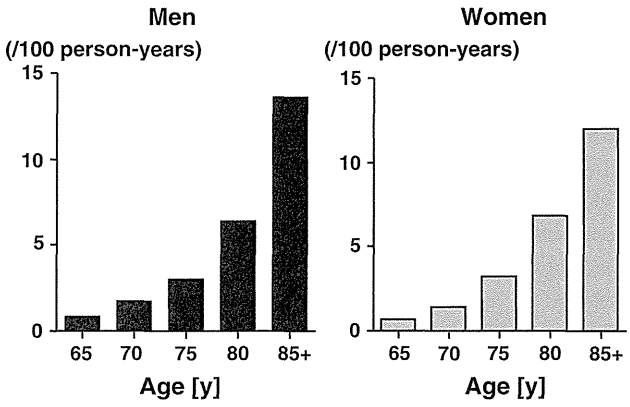

Fig. 2 Incidence of disability according to age and gender

6.36/100 p-y, and 13.54/100 p-y in 65–69-, 70–74-, 75–79-, 80–84-, and ≥85-year-old men, respectively. In women, the incidence of disability was 0.71/100 p-y, 1.40/100 p-y, 3.25/100 p-y, 6.85/100 p-y, and 12.01/100 p-y in the age ranges of 65–69, 70–74, 75–79, 80–84, and 85 or more years, respectively (Table 4).

Cox's proportional hazard regression analysis showed that occurrence of disability was significantly influenced by age, body build, and regional differences, but not gender (age, +1 years: hazard ratio 1.13, 95 % confidence interval 1.12–1.15, $p < 0.001$; sex, vs. female: 1.13, 0.97–1.31, $p = 0.125$; body build: emaciation: 1.24, 1.01–1.53, $p = 0.041$; body build; obesity: 1.36, 1.08–1.71, $p = 0.009$; residence, vs. living in rural areas: 1.59, 1.37–1.85, $p < 0.001$).

Discussion

Using the data of the LOCOMO study, we determined the incidence of disability and identified age, emaciation, obesity, and residence in rural areas as risk factors for the occurrence of disability. More specifically, we integrated data collected from subjects aged 65 and older in individual cohorts established in nine regions across Japan to determine the incidence of disability in the specified regions. We found an association between various risk factors and disability; these include age, emaciation, and obesity, as well as residence in rural areas.

The LOCOMO study was the first nation-wide prospective study to track a large number of the subjects from several population-based cohorts. The LOCOMO study aimed to integrate information from these cohorts, to prevent musculoskeletal diseases and subsequent disability. The data shed light on the prevalence and characteristics of targeted clinical symptoms such as knee pain or lumbar pain, or defined diseases such as knee osteoarthritis (KOA), lumbar spondylosis (LS), and osteoporosis (OP), as well as their prognosis in reference to either mortality or chances of developing a disability. In the present study, we also

Table 4 Hazard ratios (HRs) of potential risk factors for the occurrence and non-occurrence of disability

Disability (occurrence vs. non-occurrence)				
Explanatory variable	Reference	HR	95 % confidence interval	*p*
Age (years)	+1 year	1.13	1.12–1.15	<0.001***
Gender	0: men, 1: women	1.13	0.97–1.31	0.125
Body build	0: 18.5 ≤ BMI ≤ 27.5, 1: BMI < 18.5	1.24	1.01–1.53	0.041*
	0: 18.5 ≤ BMI ≤ 27.5, 2: BMI >27.5	1.36	1.08–1.71	0.009**
Type of residential area	0: urban area, 1: rural area	1.59	1.37–1.85	<0.001***

BMI body mass index

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

compared the above-mentioned symptoms, diseases, and prognoses between regions.

The overall incidence of disability among individuals aged 65 years and older was 3.58/100 person-years. When results from the present study are applied to the total age-sex distribution derived from the Japanese census in 2010 [1], it could be assumed that 1,110,000 people (410,000 men and 700,000 women) aged 65 years and older are newly affected by disability and require support. It has been reported that the total number of subjects who were certified as needing care increases annually [4]; however, few of these reports estimate the number of newly certified cases through a population-based cohort. Clarifying the incidence of disability and its risk factors was viewed as the first step toward preventing its occurrence.

Emaciation and obesity were both identified as risk factors for disability; thus, there appears to be a U-shaped association between BMI and disability as well as between BMI and mortality [8, 9]. According to the recent National Livelihood Survey, the leading cause of disabilities that require support and long-term care is cardiovascular disease (CVD), followed by dementia, senility, osteoarthrosis, and fractures [4]. Obesity is an established risk factor for chronic diseases, including hypertension, dyslipidemia, and diabetes mellitus, which increase the risk for CVD [10]; in turn, CVD causes ADL-related disabilities in older adults. In addition, numerous reports have shown an association between overweight or obesity and KOA [11–17]. In previous reports, we found a significant association between BMI and not only the presence of KOA, but also the occurrence and progression of KOA [18, 19]. In addition, emaciation is an established risk factor for OP and OP-related fractures [20]. OP might be related to low nutrition due to chronic wasting diseases.

The current study also found an association between living in a rural area and the occurrence of disability. There have been reports of regional differences in the certification rate of disability in Japan. For instance, Kobayashi reported a prefectural difference in the certification rate of disability, which was particularly prominent among individuals aged 75 years and older at lower nursing care levels in the long-term care insurance system [21]. In addition, Shimizutani et al. [22] pointed out that the financial condition of the insurer influenced the certification rate of disability. Further, Nakamura found that the certification of lower care levels was influenced by social and/or individual factors, such as the type of service provider, the application rate, and number of medical treatment recipients. However, certification of advanced nursing care levels was influenced by CVD and lifestyle-related diseases [23].

Other than differences in the social backgrounds of individuals in each prefecture, we posited that regional differences (rural or urban) in the occurrence of disability might be due to differences in the frequency of diseases and ailments that cause disability in each area. The prevalence of musculoskeletal diseases, such as KOA and LS, differs among mountainous, coastal, and urban areas [24]. Evidence also exists for regional differences in the incidence of hip fractures [25–27]. It was also found that mortality and incidence of ischemic stroke, which is related to CVD, was higher in the northeastern than in the southwestern part of Japan [28]. However, there is currently no information on regional differences in dementia prevalence and incidence in Japan. In general, differences in the frequency of diseases causing disability might influence regional differences in disability rates. In relation to this, in a future study on follow-up data from the LOCOMO study, it might be necessary to collect information on the prevalence and frequency of diseases that cause disability, such as musculoskeletal diseases, CVD, and dementia. This future study should also attempt to clarify mutual associations among risk factors for disability, so as to inform the development of measures for its primary prevention.

Despite its contribution to existing knowledge, the present study has several limitations. First, its sample does not truly represent the entire Japanese population, because our cohorts were not drawn from the northernmost and southernmost parts of Japan (e.g., Okinawa prefecture or Hokkaido prefecture). This limitation must be taken into consideration, especially when determining the generalisability of the results. However, the LOCOMO study is the first large-scale, population-based prospective study with approximately 9,000 participants aged 65 years and older. Second, data collected from the cohorts were not uniform, as certain information was obtained from some participants, but not others. For example, the X-ray examinations of subjects' knees were performed in Tokyo-1, Wakayama-1, Wakayama-2, Niigata, and Mie; lumbar spine X-ray examinations were performed in Tokyo-1, Wakayama-1, Wakayama-2, Hiroshima, and Mie. Therefore, we could not evaluate the presence or absence of KOA, LS, or OP as a possible cause of disability by using the data of the entire LOCOMO study. Further investigation following the integration of information on musculoskeletal disorders would enable us to evaluate all the factors that are associated with disability.

Nevertheless, our study has several strengths. As mentioned above, the large sample size is the study's biggest strength. The second strength is that we collected data from nine cohorts across Japan, which enabled us to compare regional differences in the incidence of disability. In addition, the variety of measures and assessments used in this study enabled us to collect a substantial amount of detailed information. However, given the fact that not all of the measures were administered in all cohorts, regional selection bias in the analysis should be considered when interpreting the results.

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Conflict of interest All authors declare no conflicts of interest.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Low free testosterone is associated with loss of appendicular muscle mass in Japanese community-dwelling women

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Aim: Sarcopenia accelerates frailty syndrome, and adversely affects activities of daily living and quality of life. The aim of the present study was to assess longitudinal relationships between baseline androgen and muscle mass changes in Japanese women.

Methods: Data were collected from 539 community-dwelling, Japanese women aged 40–79 years at baseline who participated in both baseline and follow-up examinations of a longitudinal study of aging (mean duration 8.3 years). Appendicular skeletal muscle mass was measured with dual-energy X-ray absorptiometry at baseline and follow-up examinations. The cut-off point for sarcopenia was a skeletal muscle index (appendicular skeletal muscle mass/height^2) <5.46 kg/m^2. Participants with sarcopenia at baseline were excluded. Thus, 430 women were included. Total testosterone, free testosterone and dehydroepiandrosterone-sulphate were measured by radioimmunoassay at baseline. The androgens were categorized into three groups by serum levels. Multiple logistic regression models were fit to determine the associations between androgens and sarcopenia while controlling for baseline age, body mass index, leisure-time physical activity, nutritional intakes (total energy, total protein, vitamin D), serum C-reactive protein levels, medical histories (heart disease, osteoporosis, rheumatoid arthritis), menopause and smoking habit.

Results: The fully adjusted odds ratio of sarcopenia for the low-free testosterone group (<0.7 pg/mL) compared with the high-free testosterone group (≥1.2 pg/mL) was 3.59 (95% confidence interval 1.25–10.34). Sarcopenia was not significantly related to total testosterone or dehydroepiandrosterone-sulphate.

Conclusion: A low-free testosterone level appears to be a significant predictor of the risk for loss of appendicular muscle in Japanese women. **Geriatr Gerontol Int 2015; 15: 326–333.**

Keywords: aging, dual-energy X-ray absorptiometry, epidemiology, longitudinal study, sarcopenia.

Introduction

Sarcopenia, which is the degenerative loss of skeletal muscle mass and strength associated with aging, accelerates frailty syndrome, and leads to deterioration of activities of daily living and quality of life.[1–3] Development of preventive measures for sarcopenia is essential for extending healthy life expectancy. The European Working Group on Sarcopenia in Older People assumed that muscle loss is a required component for the diagnosis of sarcopenia, and suggested that muscle loss is a symptom of deterioration in muscle strength and physical performance.[4] Estimation of the risks for muscle loss appears to be necessary for developing steps to prevent sarcopenia.

The etiology of sarcopenia is assumed to be multifactorial, including factors such as aging, diseases, nutritional deprivation and inactivity.[4] A low circulating level of androgens is considered to be one of the risks for sarcopenia. In men, cross-sectional and longitudinal studies have reported that a low level of testosterone, which promotes muscle protein anabolism, is associated with aging-related muscle loss.[5–8] In contrast, just a few cross-sectional studies have reported an association between the serum testosterone level and lean body mass in postmenopausal women.[9–11] Although testosterone is associated with physical characteristics in women, no longitudinal epidemiological studies have

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been published showing that circulating testosterone levels are associated with prospective decreases in muscle mass, and it is unknown whether testosterone is useful as a biomarker of sarcopenia. Furthermore, dehydroepiandrosterone (DHEA), which is an adrenal androgen in humans, could be associated with human longevity.[12] A low serum DHEA-sulphate (DHEA-S) level is also associated with frailty in older adults.[13,14] Circulating DHEA levels might be associated with muscle mass.

The aim of the present study was to determine whether circulating androgen levels predict muscle loss in middle-aged and elderly Japanese women. Thus, muscle loss with aging was assessed using 8-year follow-up examinations and dual-energy X-ray absorptiometry (DXA) in middle-aged and elderly Japanese women. Serum testosterone and DHEA-S levels were also evaluated to determine the associations between muscle loss and androgen levels in community-living, middle-aged and elderly Japanese women in a longitudinal analysis.

Methods

Participants

The participants in the present study were from the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA), which involves population-based biennial examinations of a cohort of approximately 2300 persons. The participants in the NILS-LSA were randomly selected from registered residents, and stratified by both decade of age and sex. The NILS-LSA is a comprehensive and interdisciplinary study to observe age-related changes, and consists of various gerontological and geriatric measurements, including medical examinations, blood chemical analyses, body composition, anthropometry, nutritional analysis, psychological tests, physical function and physical activity.[15] The study protocol was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology, and written, informed consent was obtained from all participants.

The baseline participants of the present study were 894 women aged 40–79 years who completed the first wave examinations of NILS-LSA between November 1997 and April 2000. Of these, 539 (60.3%) participated in the 8-year follow-up examinations (NILS-LSA 5th wave examination; from July 2006 to July 2008). Participants with sarcopenia in the first wave examination were excluded to examine the longitudinal association between the onset of sarcopenia and circulating androgen levels. Participants with a current history of oophorectomy and estrogen or progesterone preparation users were excluded, because these factors might affect sex hormone metabolism.[16] Participants with a current medical history of stroke were also excluded. Finally, 430 women were the participants for the present study.

Blood sampling and measurements of androgen levels

Blood samples were taken between 08.00 and 09.00 hours, separated immediately by centrifugation at 2000 *g* for 15 min, and sera were frozen and stored in a deep freezer (–80°C). Samples were transferred to the laboratory (SRL, Tokyo, Japan) for measurements of total testosterone (TT), free testosterone (FT), DHEA-S, estradiol and C-reactive protein levels.

The serum levels of TT (ng/dL), FT (pg/mL), DHEA-S (ng/mL) and estradiol (pg/mL) were also measured with a radioimmunoassay (RIA) using commercially available kits (Diagnostic Products Corporation, Los Angeles, CA, USA). The interassay coefficients of variation were less than 15% for both kits, according to the manufacturer's information. The serum C-reactive protein level was measured by nephelometry (NA Latex CRP kit; Dade Behring, Tokyo, Japan).

Definition of sarcopenia

Appendicular skeletal muscle mass (kg) and fat mass were assessed by DXA (QDR-4500; Hologic, Bedford, MA, USA). Appendicular skeletal muscle mass is equal to the appendicular fat-free mass minus bone mineral contents, and it is assumed to be an index of the amount of muscle mass.

The skeletal muscle index (SMI) was used to evaluate sarcopenia.[1] The SMI was calculated by appendicular skeletal muscle mass divided by height squared (kg/m^2). Sarcopenia was defined as muscle mass that was minus two standard deviations below the mean for young adult healthy people.[1] In the present study, the cut-off point for sarcopenia was SMI <5.46 kg/m^2 (muscle mass minus 2 standard deviations below the mean for young adult healthy Japanese women).[17] Sanada *et al.* also measured appendicular muscle mass with DXA with the same model (QDR-4500; Hologic) used in the present study.[17]

Other parameters

Height and weight were measured using a digital scale. Body mass index (BMI; kg/m^2) was calculated by weight divided by height squared. Medical history, smoking habit, and use of medications were assessed with questionnaires and confirmed by a physician at the medical examinations. All prescribed and non-prescribed medications used during the previous 2 weeks were documented and brought by the participants; the physicians confirmed and coded them. Trained interviewers used a questionnaire, and asked the participants about the