

Vasomotor symptoms, sleep problems, and depressive symptoms in community-dwelling Japanese women

Makiko Tomida¹, Rei Otsuka¹, Chikako Tange¹, Yukiko Nishita¹, Tomomi Kimura², Matthias Stoelzel³, Keiko Tanaka-Amino⁴, Hiroshi Shimokata^{1,5} and Masakazu Terauchi⁶

¹Department of Epidemiology of Aging, National Center for Geriatrics and Gerontology, Aichi, Japan

²Astellas Pharma Inc., Northbrook, Illinois, USA

³Astellas Pharma Europe B.V., Leiden, Netherlands

⁴Astellas Pharma Inc., Tokyo, Japan

⁵Graduate School of Nutritional Sciences, Nagoya University of Arts and Sciences, Aichi, Japan

⁶Department of Women's Health, Tokyo Medical and Dental University, Tokyo, Japan

Abstract

Aim: To assess prevalence and characteristics of vasomotor symptoms in community-dwelling Japanese women.

Methods: These were cross-sectional analyses using data from the National Institute for Longevity Sciences-Longitudinal Study of Aging. The main outcome measures were prevalence and severity of hot flashes and sweating. Associations between hot flashes/sweating (slight, moderate, or severe vs none) and sleep problems were explored using logistic regression, with and without adjustment for age, daily physical activity, and number of urinations/night. Associations between hot flashes/sweating and sleep problems, depressive symptoms, and dietary variables were explored in logistic regression models or general linear models.

Results: A total of 1152 women between 40 and 91 years of age were enrolled. Hot flashes were reported by 24.5% of participants; with prevalence and severity highest in those 50–54 years or 2–5 years postmenopause. Sleep problems were reported 15 percentage points more frequently by women who reported hot flashes than by those without hot flashes. Adjusted odds ratios [95% CI] for difficulty in falling asleep and difficulty in sleeping through were 2.09 [1.565–2.796] and 2.07 [1.549–2.763]), respectively. Also, hot flashes were associated with higher risk of depressive symptoms (adjusted odds ratio [95% CI]: 2.99 [2.07–4.32]) and lower life satisfaction, self-esteem, and self-rated health status. A similar pattern was observed in women with and without sweating. No associations were found between hot flashes and dietary factors.

Conclusions: Clear associations were found between hot flashes and sleeping problems, even after adjusting for potential confounding factors. Women who reported hot flashes also reported worse mental and physical health than those who did not report hot flashes.

Key words: depressive symptoms, hot flashes, Japan, menopause, sleep.

Introduction

Menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity.¹ In 2012, the Japan Nurses' Health

Study, examining data from 24 152 pre- and postmenopausal Japanese women ≥ 40 years of age, reported that the median age of menopause was 52.1 years.² According to data from the Study of Women's Health Across the Nation (SWAN), a multiracial/multiethnic

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Correspondence: Dr Rei Otsuka PhD, National Center for Geriatrics and Gerontology, 7-430 Morioka-cho, Obu, Aichi 474-8511, Japan.

Email: otsuka@ncgg.go.jp

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observational study, vasomotor symptoms (VMS) characterized by hot flashes (also known as hot flushes) and/or night sweats are experienced by up to 80% of postmenopausal women during the menopausal transition.³ VMS are also relatively common in older women, for example, the Heart and Estrogen/Progestin Replacement Study in women with a mean age of 67 years and a mean of 18 years since last menstrual period found that 16% of women reported frequent hot flashes.⁴ There are, however, limited data examining the prevalence of VMS in Japan in women over 70 years of age.

In addition to discomfort, moderate-to-severe VMS are associated with depressive symptoms and sleep problems,⁵ which can significantly affect the quality of life.^{6–10} Sleeping disorders often cluster together with hot flashes^{11,12} and night sweats¹³; however, the impact of VMS on quality of life, and in particular on sleep problems has not been fully examined in a Japanese population.^{11,14}

The standard of care for VMS associated with menopause is hormone therapy (HT) with combined estrogen and progestogen, or estrogen alone.¹⁵ Nonhormonal therapies include, lifestyle changes, mind–body techniques, and dietary management and supplements. Only a few studies of women in Japan have examined the association between diet and VMS, and the findings have been inconsistent.^{16,17}

The objective of this study was to present descriptive data on the prevalence of VMS, and to explore clinical and physiological characteristics of Japanese women in the general population using a representative sample with VMS. Associations between VMS and sleep problems, depressive symptoms, and diet were also explored.

Methods

Study design

These were cross-sectional analyses using data from the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA). A priori hypothesis was not defined for this study.

Data source and study population

Details of the NILS-LSA study have been reported elsewhere^{18,19}; in summary, this project aimed to assess the normal aging process using detailed questionnaires and medical checkups, anthropometric measurements, physical fitness tests, and nutritional

examinations. Participants were randomly selected from basic resident registers of Ōbu-city and Higashiura-town, Aichi Prefecture, a central Japanese region with a typical Japanese lifestyle, and were age-decade- and sex-stratified men and women aged 40–79 years in their first participation. Participants were sent a letter inviting them to an explanatory meeting. Participants were limited to those who understood all examination procedures and provided written informed consent; therefore, there was no screening of participants.

The first wave of the NILS-LSA was carried out from November 1997 to April 2000, with follow-up every 2 years. When participants ≤ 79 years could not be followed up (e.g., they transferred to another area, dropped out for personal reasons, or died), new age-decade- and sex-matched participants were randomly recruited. Participants 40 years of age were also newly recruited every year. Therefore, each study wave included nearly 1200 men and 1200 women. The 8th study wave was conducted at intervals of 3 years from the 7th wave without recruiting new participants. From the 1st to the 7th wave, when new participants were recruited, the percentage of those attending the explanatory meeting was generally around 30%; for those attending the explanatory meeting, almost 100% of participants agreed to participate in the actual survey. In all of the surveys from the 1st to the 8th wave, the retention rate from the previous survey to the next survey was $>80\%$. The number of cumulative examinations from the 1st to the 7th waves was 16 338, and the total number of participants from all waves was 3983. Of these participants, 955 men and women attended all examinations from the 1st to the 7th wave. The participation rate for both the 1st and 7th wave was 51.5%.

The present study examined data on women from the 7th study wave (July 2010 to July 2012), that is, 1152 community-dwelling Japanese women between 40 and 91 years of age. Written informed consent was obtained from all participants. The Ethics Committee of the National Center for Geriatrics and Gerontology approved all procedures of the NILS-LSA. The retention rate for the 7th–8th study wave was 85.4%. The number of participants who dropped out between the 7th and 8th wave included 23 who were excluded due to death or relocation.

Data collection

Hot flashes and sweating were defined by the response to questions in the Kupperman Konenki

Shogai Index (KCSI).²⁰ The KCSI belongs to Sankyobo,²¹ and is a modified version of the Kupperman Index for Japanese women, which has been widely used in clinical practice. Participants were asked about their symptoms over the past 2–3 days. Severity of each symptom was described as “None,” “Slight,” “Moderate,” or “Severe.” The presence of each symptom was defined as “With” for “Slight,” “Moderate,” or “Severe,” and “Without” for “None.” Participants were not asked about actual sweating but if they felt liable to sweating. Sleep problems were defined by the response to questions in the KCSI. Women with sleep problems were defined as those who experienced difficulty in falling asleep (slight, moderate, or severe vs none) or difficulty in sleeping through (slight, moderate, or severe vs none). Sleeping hours/day was calculated from information on the daily time schedule of semi-structured interviews.

Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D).²² This scale comprises 20 items with four options each. Responses are based on the frequency of occurrence during the past week: rarely or none of the time (<1 a day), some or a little of the time (1–2 days), occasionally or a moderate amount of the time (3–4 days), most or all of the time (5–7 days). Scores range from 0 to 60, with high scores indicating greater depressive symptoms. A total score ≥ 16 indicates clinically significant depressive tendencies.

Life satisfaction was evaluated with the Life Satisfaction Index-K,²³ a 9-item questionnaire that uses a 2- or 3-point scale for each item. Scores were calculated according to the method described by Koyano,²³ such that higher scores indicated a higher level of life satisfaction. Self-rated health was assessed by participants on a 5-point scale from “Excellent” to “Very bad.” A higher score suggests poor health. Self-esteem was evaluated with the Rosenberg Self-Esteem Scale.^{24,25} Participants responded on a 4-point scale. Data were scored according to the prescribed procedure, with higher scores indicating higher self-esteem.

Dietary intake was assessed using 3-day dietary records, completed over three continuous days (2 weekdays, 1 weekend day). Participants completed the dietary record at home. Food was weighed separately on a scale (1-kg kitchen scales; Sekisui Jushi) before being cooked or portion sizes estimated. Participants also recorded their diet using a disposable camera (27 shots; Fujifilm) by taking photos of meals before and after eating. Dietitians used these photos

to complete missing data and telephoned participants to resolve any discrepancies or obtain further information when necessary. Averages for 3-day nutrient and energy intakes were calculated according to the Standard Tables of Foods Composition 2010 in Japan²⁶ and other sources. Methods for collecting background factor variables and the categorization criteria are presented in Table 1. These variables were obtained by self-administered questionnaires or by measurement by trained staff.

Women were asked if they were receiving menopausal hormone therapy (options: “No,” “Current,” or “Previous”) and about the presence of menstruation (options: “Yes,” “No,” or “Unknown”). Women who responded to say that they had menstruation or were unsure were asked for “Change in menstruation in the last year” (options: “Yes,” “No,” or “Unknown”). Definitions of menopausal transition state are shown in Table 2. Only women who were menopausal were asked for their age (in years) at last menstruation. If age at last menstruation at the 7th study wave was unknown, age at last menstruation at the 8th study wave was used. Women who had undergone “Surgical menopause” were asked to indicate “with ovary function,” “without ovary function,” or “ovary function unknown.” This information was collected with a self-administered questionnaire. Time from menopause (defined in Table 2) was generally calculated as (age at 7th study wave) - (age at last menstruation at 7th wave). Two women were in their 40s and were using oral contraceptives or other hormonal contraception. Those who used contraceptives were classified as having menstruation. Menopausal transition state and time from menopause excluded women undergoing surgical menopause ($n = 10$) or on hormonal therapy ($n = 117$). Two women were in both categories.

Statistical analysis

Continuous measures, including age, body mass index (BMI), and body fat were summarized by descriptive statistics, with/without stratification by hot flashes and sweating. Categorical variables such as menopausal transition state and education were summarized using numbers and percentages of women with/without stratification by hot flashes and sweating.

Associations between hot flashes/sweating (slight, moderate, or severe vs none) and sleep problems were explored using a logistic regression model, with and without adjustment for age, daily physical

Table 1 Measurements

Participant characteristics	Measure
Age at last menstruation ^a	Age in years
Surgical menopause ^a	No, with ovary function, without ovary function, or ovary function unknown
Menopausal hormone therapy ^a	No, current, or previous
Drinking habit ^a	No, more than once per week for any alcoholic beverage
Current smoker	Yes or no
Education ^a	≤9, 10–12, ≥13 years of school
Annual family income ^a	<2.5 million Japanese Yen, 2.5 to <4.5 million Japanese Yen, >4.5 million Japanese Yen
Employment status ^a	Unemployed, employed
Frequency of going out ^a	At least once per day, once every 2–3 days, once a week, almost none
Meeting/talking with people ^a	At least once per day, once every 2–3 days, once a week, once a month, almost none
Number of urinations per night ^a	0, 1, 2, 3, 4, ≥5
Weight and height	Measured using WB-510, TANITA, Inc. to the nearest 0.1 kg and 0.1 cm, respectively, with participants wearing light clothing and no shoes
BMI	Calculated as the body weight in kilograms divided by the square of the height in meters
Daily physical activity	Assessed by the METs score (a multiple of the resting metabolic rate), obtained through participant interviews with trained interviewers using a semi-quantitative assessment method to assess participants' levels of habitual physical activity during leisure time and on the job, and their sleeping hours ²⁷
Body fat (% or kg)	Assessed by dual-energy X-ray absorptiometry (QDR-4500; Hologic)
Systolic and diastolic blood pressure	Measured in mmHg, using the upper right arm with participants in a seated position using an automatic blood pressure analyzer (BP-204RV, Colin, Inc.)

^aMeasurements were collected using self-reported questionnaires and confirmed by medical doctors or trained staff. and Abbreviations: BMI, body mass index; METs, metabolic equivalents.

activity, and number of urinations/night. Associations between hot flashes/sweating and psychological outcomes (CES-D score, CES-D score cut-off, Life Satisfaction Index-K, self-rated health score, and self-esteem scale) were also explored in logistic regression models or general linear models, with and without adjustment for age, daily activity, and education. Associations between hot flashes/sweating and dietary variables were explored using general linear models, with adjustment for age, education, smoking, drinking, and daily activity.

In the multiple logistic regression model, covariates were incorporated based on clinical judgment and the literature, associated with the outcome at $p < 0.10$ as the criterion for retention, confirming that the covariates were associated with the outcomes. In addition, to statistically confirm the retention of covariates in the multiple logistic regression model, we forced age into the model and then used a stepwise method to ensure that each covariate was selected. Stepwise procedures were used to eliminate unrelated predictors to better estimate the coefficients for the remaining factors and to obtain better fitting models. Interactions were not examined in this study. To assess the fit of multivariate models, the

Akaike Information Criterion (AIC) and Hosmer-Lemeshow test were used for multivariate logistic regression, and the general linear model was assessed by R^2 (for the general linear model, R^2 was calculated and added to each table). The adjusted model had a smaller AIC value than the unadjusted model, and the Hosmer-Lemeshow test confirmed that the model was a good fit with $p > 0.05$.

In the model, hot flashes and sweating were treated as explanatory variables. In the analysis of nutrition, hot flashes and sweating were considered as outcomes, but because these were cross-sectional analyses, we were examining associations and used them as explanatory variables in the analyses.

All statistical analyses were performed using Statistical Analysis System software version 9.3 (SAS Institute).

Results

In total, 1152 women participating in the NILS-LSA 7th study wave were included. There were no exclusions. The median age (interquartile range; Q3–Q1) was 61 years (50–72) (Table 3). The median age at

Table 2 Definitions of menopausal transition state and time from menopause

Variable	Definition
Menopausal transition state	
Premenopause	Women responded “Yes” or “Unknown” to “Presence of menstruation” at 7th study wave, AND responded “No” or “Unknown” to “Change in menstruation in the last year,” AND NOT surgical menopause or on hormonal therapy
Perimenopause	Women responded “Yes” to “Change in menstruation in the last year” at 7th study wave AND responded “Yes” or “Unknown” to the question for “Presence of menstruation,” AND NOT surgical menopause or on hormonal therapy
Postmenopause	Women responded “No” to “Presence of menstruation” at 7th study wave AND NOT surgical menopause or on hormonal therapy
Time from menopause ^a	
If women reported “No” to “Presence of menstruation” at the 7th wave	(Age at 7th study wave) – (age at last menstruation ^b at 7th wave)
If women reported “Yes” or “Unknown” to “Presence of menstruation” at the 7th wave AND reported “No” to “Presence of menstruation” at the 8th wave	(Age at 7th study wave) – (age at last menstruation at 8th wave)
If women reported “Yes” or “Unknown” to “Presence of menstruation” at the 7th wave AND reported “Yes” or “Unknown” to “Presence of menstruation” at the 8th wave	< –3 years

^aWomen undergoing surgical menopause or on hormonal therapy were excluded. and ^bIf age at last menstruation at the 7th wave was unknown, age at last menstruation at the 8th wave was used.

menopause was 50 years (Figure S1). In total, 119 (10.3%) women had undergone hysterectomy and 275 (23.9%) were undergoing treatment for hypertension. Current or previous menopausal HT (for osteoporosis or menopausal disorder) was reported by only 1.0% or 5.3% of the participants, respectively.

No difference in age at menopause by age group (40–49, 50–59, 60–69, 70–79, and 80+) was observed except for a lower age at menopause in the youngest age group (data not shown).

Characteristics of women reporting hot flashes or sweating: Reports of unadjusted analyses

Age at the time of the survey ranged from 40 to 91 years, and 282 (24.5%) of women reported hot flashes. The severity of hot flashes was: none: $n = 870$ (75.5%); slight: $n = 168$ (14.6%); moderate: $n = 94$ (8.2%); and severe: $n = 20$ (1.7%). The severity of sweating was none: $n = 579$ (50.3%); slight: $n = 190$ (16.5%); moderate: $n = 280$ (24.3%); and severe: $n = 103$ (8.9%). In unadjusted analyses, women with hot flashes were slightly younger than those without hot flashes, whereas women were of similar age whether or not they experienced sweating (Table 3).

Women with hot flashes or sweating were slightly heavier and had a slightly higher percentage of body fat than those without these symptoms.

The proportion of premenopausal women was slightly lower in women reporting hot flashes or sweating versus those without these symptoms. There was a higher proportion of women currently on menopausal HT in the group with hot flashes versus those without hot flashes, but a lower proportion currently on menopausal HT in the group reporting sweating versus those without this symptom. Women with hot flashes were better educated than those not reporting hot flashes.

Although there were small differences in median systolic blood pressure between women who did/did not report sweating, age at menopause, BMI, median diastolic blood pressure, current smoking status, and frequency of going out and meeting/talking with people were similar between groups. No notable differences were observed between those with and without hot flashes with regards to these factors. Women who reported hot flashes or sweating had a higher prevalence of all other KCSI symptoms compared with those who did not (Table S1).

Table 3 Unadjusted results of women with/without hot flashes or sweating

	Total (<i>n</i> = 1152)	Hot flashes		Sweating	
		With (<i>n</i> = 282)	Without (<i>n</i> = 870)	With (<i>n</i> = 573)	Without (<i>n</i> = 579)
Age, years, mean (SD)	61.4 (12.90)	59.6 (12.16)	61.9 (13.09)	61.6 (12.68)	61.1 (13.12)
Median (Q3–Q1)	61 (50–72)	57 (50–69)	62 (50–73)	60 (51–71)	61 (49–72)
Age at last menstruation, years, mean (SD)	49.6 (4.52)	50.0 (4.57)	49.5 (4.49)	49.7 (4.59)	49.5 (4.45)
<i>n</i>	841	207	634	431	410
Median (Q3–Q1)	50 (48–52)	50 (48–53)	50 (48–52)	50 (48–52)	50 (48–52)
Range	24–63	24–63	26–60	24–60	32–63
Menopausal transition state, <i>n</i> (%)					
Premenopause	160 (13.9)	36 (12.8)	124 (14.3)	69 (12.0)	91 (15.7)
Perimenopause	136 (11.8)	34 (12.1)	102 (11.7)	64 (11.2)	72 (12.4)
Postmenopause	727 (63.1)	177 (62.8)	550 (63.2)	377 (65.8)	350 (60.5)
Surgical menopause					
With ovary function	68 (5.9)	15 (5.3)	53 (6.1)	30 (5.2)	38 (6.6)
Without ovary function	42 (3.7)	13 (4.6)	29 (3.3)	25 (4.4)	17 (2.9)
Ovary function unknown	9 (0.8)	3 (1.1)	6 (0.7)	5 (0.9)	4 (0.7)
Unknown	10 (0.9)	4 (1.4)	6 (0.7)	3 (0.5)	7 (1.2)
Menopausal hormone therapy, ^a <i>n</i> (%)					
Current	12 (1.0)	6 (2.1)	6 (0.7)	4 (0.7)	8 (1.4)
Previous	61 (5.3)	15 (5.3)	46 (5.3)	36 (6.3)	25 (4.3)
BMI in kg/m ² , mean (SD)	22.3 (3.4)	23.0 (4.1)	22.1 (3.2)	23.0 (3.8)	21.6 (2.9)
Median (Q3–Q1)	21.8 (20.0–24.0)	22.0 (20.2–25.3)	21.7 (19.9– 23.7)	22.3 (20.4–24.8)	21.2 (19.6– 23.3)
Range	13.5–43.6	15.0–42.5	13.5–43.6	15.0–43.6	13.5–33.3
Body fat in %, mean (SD)	31.2 (5.3)	32.2 (5.6)	30.9 (5.2)	31.8 (5.4)	30.6 (5.2)
<i>n</i>	1138	278	860	566	572
Median (Q3–Q1)	31.4 (27.5–34.8)	32.0 (27.9–35.8)	31.0 (27.4– 34.5)	31.9 (27.9–35.3)	30.7 (27.2– 34.2)
Range	12.2–47.2	18.0–46.8	12.2–47.2	16.7–47.2	12.2–43.9
Body fat in kg, mean (SD)	17.1 (5.3)	18.3 (6.1)	16.7 (4.9)	18.0 (6.0)	16.2 (4.4)
<i>n</i>	1138	278	860	566	572
Median (Q3–Q1)	16.2 (13.6–19.7)	17.2 (14.4–21.6)	15.9 (13.4– 19.3)	16.8 (14.2–20.7)	15.7 (13.2– 18.9)
Range	5.0–52.0	7.0–49.5	5.0–52.0	6.9–52.0	5.0–32.6
SBP, mmHg, mean (SD)	117.3 (18.2)	118.5 (18.2)	116.8 (18.2)	119.3 (18.2)	115.2 (18.0)
<i>n</i>	1150	282	868	573	577
Median (Q3–Q1)	114 (103–128)	115 (104–131)	114 (103– 128)	117 (105–131)	112 (101– 126)
Range	76–177	79–176	76–177	76–176	77–177
DBP, mmHg, mean (SD)	71.0 (10.5)	72.0 (10.3)	70.7 (10.6)	72.3 (10.4)	69.8 (10.5)
<i>n</i>	1150	282	868	573	577
Median (Q3–Q1)	70 (64–77)	72 (64–79)	70 (63–77)	71 (65–79)	69 (62–76)
Range	46–110	49–99	46–110	49–110	46–105
Education, <i>n</i> (%)					
≤9 years	224 (19.4)	39 (13.8)	185 (21.3)	113 (19.7)	111 (19.2)
10–>12 years	492 (42.7)	128 (45.4)	364 (41.8)	253 (44.2)	239 (41.3)
>13 years	436 (37.9)	115 (40.8)	321 (36.9)	207 (36.1)	229 (39.6)
Annual income, <i>n</i> (%)					
<2.5 million Japanese Yen	157 (13.6)	44 (15.6)	113 (13.0)	66 (11.5)	91 (15.7)
2.5 to <4.5 million Japanese Yen	299 (26.0)	66 (23.4)	233 (26.8)	158 (27.6)	141 (24.4)
≥4.5 million Japanese Yen	663 (57.6)	166 (58.9)	497 (57.1)	334 (58.3)	329 (56.8)
Unknown	33 (2.9)	6 (2.1)	27 (3.1)	15 (2.6)	18 (3.1)
Drinking habit, ^b <i>n</i> (%)	277 (24.0)	72 (25.5)	205 (23.6)	139 (24.3)	138 (23.8)

(Continues)

Table 3 Continued

	Total (<i>n</i> = 1152)	Hot flashes		Sweating	
		With (<i>n</i> = 282)	Without (<i>n</i> = 870)	With (<i>n</i> = 573)	Without (<i>n</i> = 579)
Current smoker, <i>n</i> (%)	44 (3.8)	10 (3.6)	34 (3.9)	19 (3.3)	25 (4.3)
Employment status, <i>n</i> (%)					
Unemployed	566 (49.1)	148 (52.5)	418 (48.1)	279 (48.7)	287 (49.6)
Employed ^c	586 (50.9)	134 (47.5)	452 (52.0)	294 (51.3)	292 (50.4)
Frequency of going out, <i>n</i> (%)					
At least once/day	879 (76.3)	209 (74.1)	670 (77.0)	434 (75.7)	445 (76.9)
Once every 2–3 days	243 (21.1)	60 (21.3)	183 (21.0)	122 (21.3)	121 (20.9)
Once a week	24 (2.1)	10 (3.6)	14 (1.6)	13 (2.3)	11 (1.9)
Almost none	6 (0.5)	3 (1.1)	3 (0.3)	4 (0.7)	2 (0.4)
Meeting/talking with people, <i>n</i> (%)					
At least once/day	630 (54.7)	150 (53.2)	480 (55.2)	307 (53.6)	323 (55.8)
Once every 2–3 days	366 (31.8)	88 (31.2)	278 (32.0)	189 (33.0)	177 (30.6)
Once a week	120 (10.4)	31 (11.0)	89 (10.2)	58 (10.1)	62 (10.7)
Once a month	27 (2.3)	11 (3.9)	16 (1.8)	16 (2.8)	11 (1.9)
Almost none	9 (0.8)	2 (0.7)	7 (0.8)	3 (0.5)	6 (1.0)

Note: Number of subjects for each variable are as shown at the top of the table unless otherwise indicated.; Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; Q, quartile; SBP, systolic blood pressure.; ^aMenopausal hormone therapy for osteoporosis or menopausal disorder.; ^bMore than once/week for any alcoholic beverage. and ^cEmployees, employers, and self-employed workers.

Prevalence of hot flashes and sweating

The prevalence of hot flashes was largely dependent on age and time from menopause (Figure 1); however, the prevalence of sweating did not show a strong link to menopausal transition state. The prevalence of hot flashes started to increase at 45–49 years or up to 3 years prior to menopause, and continued to be relatively high until 55–59 years or 2–5 years since menopause. Specifically, the prevalence of hot flashes was highest in the 50–54 years group (45.2%), followed by the 55–59 years group (31.7%). Prevalence was 18.6%–21.4% in older age groups; no decreasing trend was observed with increasing age in these groups, indicating persistence of hot flashes in about 20% of women over the age of 60 years and more than 5 years beyond their final menstrual period.

In unadjusted analyses, self-reported severity of hot flashes was also associated with age (Figure 2): the proportions of moderate or severe hot flashes were highest in the 50–54 years group.

Association with sleeping problems

Half the women with hot flashes reported “Difficulty in falling asleep” and “Difficulty in sleeping through” according to symptoms recorded in the KKSI; sleep problems were reported 15 percentage points more frequently by women who reported hot flashes than by those without hot flashes: 47.9% versus 33.2% for “Difficulty in falling asleep” and 50.7% versus 34.5%

for “Difficulty in sleeping through,” respectively (Table 4). Mild problems in “Difficulty in falling asleep” were reported by 31.6% of women with hot flashes versus 18.7% without hot flashes. The proportions of women reporting moderate or severe sleep problems were similar between groups.

When adjusted for age, daily physical activity, and number of urinations/nights, sleeping hours were similar between women with and without hot flashes, and between women with and without sweating (Table S2).

Association with psychological outcomes

Women reporting hot flashes reported a higher CES-D score (Table 4). The age-adjusted mean score (SE) was 10.0 (0.43) in women with hot flashes and 6.7 (0.24) in those without hot flashes. When the CES-D score was categorized at a cut-off value of 16 (indicating risk of clinically significant depression), the age-adjusted odds ratio for hot flashes (95% CI) was 2.99 (2.07–4.32) for elevated depressive symptom score. Women with hot flashes showed lower life satisfaction, lower self-esteem, and poorer self-rated health status versus those without hot flashes. The pattern in women with and without sweating was similar to that seen in women with or without hot flashes. When analyzed by hot flash severity, trends in psychological scores were not obvious (Table S3).

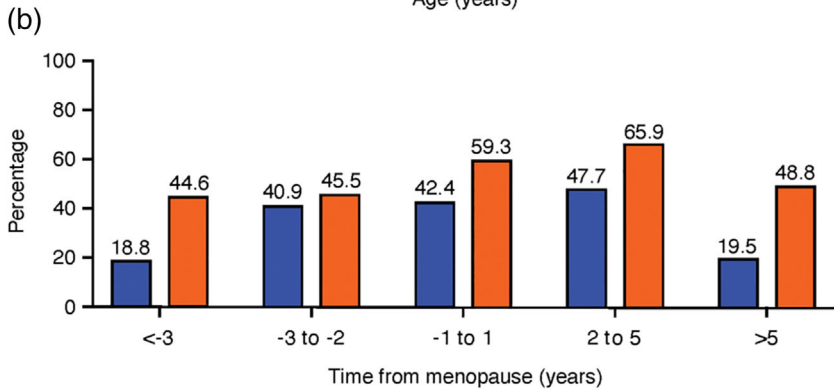
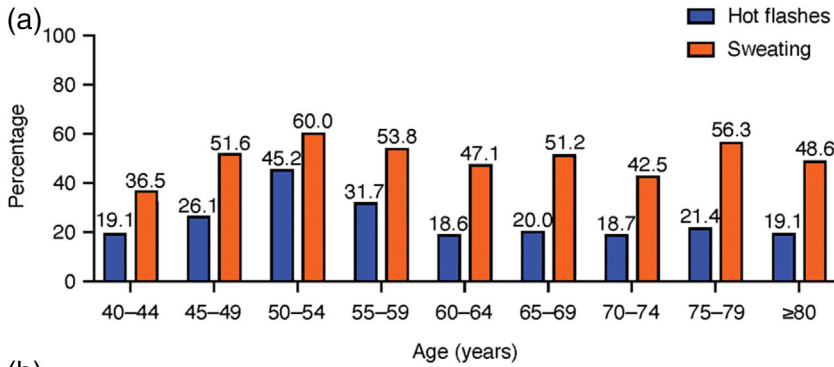


Figure 1 Prevalence of hot flashes and sweating by (a) age group and (b) time from menopause

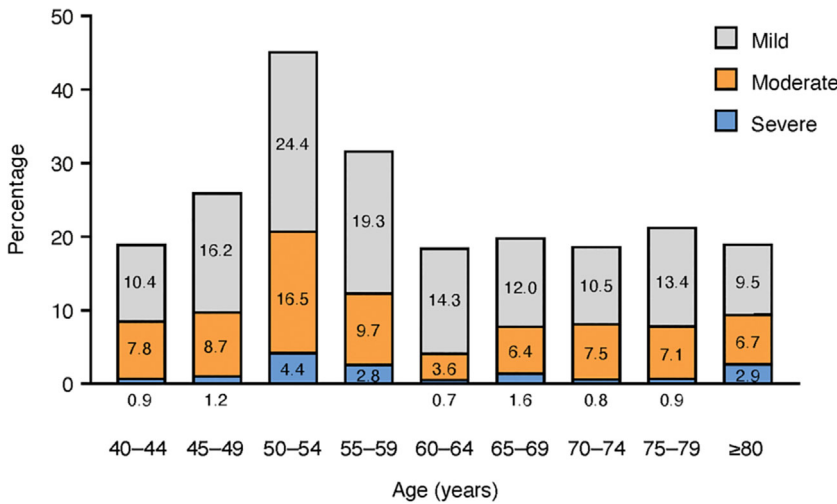


Figure 2 Prevalence of mild, moderate, and severe hot flashes by age group

Association with dietary factors

No association was found between hot flashes and any dietary factors studied, with/without adjusting for potential confounding factors (age, education, smoking, drinking, and daily activity; Table S4). When adjusted for age, education, smoking, drinking, and daily activity, women reporting sweating consumed slightly more fruit (adjusted average:

156.4 g/day) than women without sweating (132.7 g/day, $p = 0.0002$). In addition, in adjusted analyses, women reporting sweating had a slightly higher carbohydrate intake (mean 253.1 g/day) than women without sweating (mean 247.0 g/day, $p = 0.0347$), and women reporting sweating had a slightly higher meat intake (mean 72.6 g/day) than women without sweating (mean 68.3 g/day, $p = 0.0432$).

Table 4 Sleeping problems and psychological outcomes in women with/without hot flashes and sweating (unadjusted and adjusted results)

		Hot flashes		Sweating	
		With (<i>n</i> = 282)	Without (<i>n</i> = 870)	With (<i>n</i> = 573)	Without (<i>n</i> = 579)
Difficulty in falling asleep, <i>n</i> (%)	None	147 (52.1)	581 (66.8)	315 (55.0)	413 (71.3)
	Any	135 (47.9)	289 (33.2)	258 (45.0)	166 (28.7)
	Mild	89 (31.6)	163 (18.7)	153 (26.7)	99 (17.1)
	Moderate	31 (11.0)	90 (10.3)	79 (13.8)	42 (7.3)
	Severe	15 (5.3)	36 (4.1)	26 (4.5)	25 (4.3)
	Unadjusted odds ratio (95% CI)	1.85 (1.41–2.43)		2.04 (1.60–2.61)	
	Adjusted odds ratio (95% CI) ^a	2.09 (1.57–2.80)		2.06 (1.60–2.67)	
Difficulty in sleeping through, <i>n</i> (%)	None	139 (49.3)	570 (65.5)	304 (53.1)	405 (69.9)
	Any	143 (50.7)	300 (34.5)	269 (47.0)	174 (30.1)
	Mild	86 (30.5)	186 (21.4)	157 (27.4)	115 (19.9)
	Moderate	42 (14.9)	85 (9.8)	80 (14.0)	47 (8.1)
	Severe	15 (5.3)	29 (3.3)	32 (5.6)	12 (2.1)
	Unadjusted odds ratio (95% CI)	1.96 (1.49–2.57)		2.06 (1.62–2.62)	
	Adjusted odds ratio (95% CI) ^a	2.07 (1.55–2.76)		2.09 (1.62–2.70)	
CES-D score ^b	Mean (SD)	9.9 (8.33)	6.8 (6.82)	8.7 (7.79)	6.4 (6.67)
	Median (Q3–Q1)	8 (3–15)	5 (2–10)	6 (3–13)	4 (2–10)
	Range	0–36	0–42	0–42	0–38
	Adjusted mean (SE)	10.0 (0.43)	6.7 (0.24)	8.7 (0.30)	6.4 (0.30)
	R ²		0.06	0.05	
CES-D score cut-off ^b	≥16, <i>n</i> (%)	64 (22.7)	86 (9.9)	101 (17.6)	49 (8.5)
	<16, <i>n</i> (%)	218 (77.3)	784 (90.1)	472 (82.4)	530 (91.5)
	Unadjusted odds ratio (95% CI)	2.68 (1.87–3.82)		2.32 (1.61–3.33)	
	Adjusted odds ratio (95% CI)	3.04 (2.10–4.40)		2.34 (1.62–3.39)	
Life satisfaction Index-K ^c	<i>n</i>	281	868	571	578
	Mean (SD)	4.8 (2.20)	5.4 (2.14)	5.0 (2.19)	5.5 (2.13)
	Median (Q3–Q1)	5 (3–6)	6 (4–7)	5 (3–7)	6 (4–7)
	Range	0–9	0–9	0–9	0–9
	Adjusted mean (SE)	4.7 (0.13)	5.4 (0.07)	5.0 (0.09)	5.5 (0.09)
	R ²		0.04	0.03	
Self-rated health score ^d	Mean (SD)	2.9 (0.61)	2.6 (0.69)	2.8 (0.65)	2.6 (0.70)
	Median (Q3–Q1)	3 (3–3)	3 (2–3)	3 (2–3)	3 (2–3)
	Range	1–4	1–5	1–4	1–5
	Adjusted mean (SE)	2.9 (0.04)	2.6 (0.02)	2.8 (0.03)	2.6 (0.03)
	R ²		0.07	0.05	
Self-esteem scale ^e	<i>n</i>	281	869	571	579
	Mean (SD)	27.2 (4.73)	28.8 (4.70)	28.0 (4.80)	28.8 (4.68)
	Median (Q3–Q1)	27 (24–30)	29 (26–32)	28 (25–31)	29 (26–32)
	Range	13–40	11–40	11–40	13–40
	Adjusted mean (SE)	27.2 (0.28)	28.8 (0.16)	28.0 (0.20)	28.8 (0.20)
R ²		0.04		0.03	

Note: Number of subjects for each variable were as described at the top unless otherwise indicated.; Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; Q, quartile.; ^aDifficulty in falling asleep and difficulty in sleeping through were adjusted for age, daily physical activity, number of urinations/night. CES-D score, CES-D score cut-off, life satisfaction Index-K, self-rated health score, and self-esteem scale were adjusted for age, daily activity, and education.; ^bScores range from 0 to 60, with high scores indicating greater depressive symptoms. A total score ≥16 indicates clinically significant depressive tendencies.; ^cThe Life Satisfaction Index-K (LSI-K) uses a 2- or 3-point scale for each item, with higher scores indicating a higher level of life satisfaction. Scores range from 0 to 9.; ^dSelf-rated health score was assessed by participants on a 5-point scale from "Excellent" to "Very bad." A higher score suggests poor health. Scores range from 1 to 5. and ^eSelf-esteem was evaluated with the Rosenberg Self-Esteem Scale, a 4-point scale, with higher scores indicating a higher level of self-esteem. Scores range from 10 to 40.

Discussion

This study of 1152 community-dwelling women aged 40–91 years from a region of Japan with a typical Japanese lifestyle adds to the literature by providing real-world data on Japanese women. In this study, the prevalence of hot flashes was 24.5%, with a peak at age 50–54 years (45.2%), or 2–5 years postmenopause (47.7%); severity of hot flashes was also highest in the 50–54 years age group. This prevalence is similar to that previously reported in a Japanese population aged 45–55 years,²⁸ but lower than in other Japanese studies, which found a prevalence of hot flashes of 36.9% (in women 50 years of age),²⁹ and 46.0% and 46.6% (in women aged 45–60 years).^{30,31} According to Melby, variations in the terminology used by Japanese women to describe hot flashes may account for differences in prevalence.²⁸

Interestingly, the prevalence of VMS reported by Japanese women appears to be lower than that reported by women from other racial and ethnic groups. For example, a study of Japanese women living in the Pacific Northwest of the United States enrolled in a healthcare system reported that 63.1% had experienced hot flashes at some point compared with 84.0% of Caucasians and that 46.7% of Japanese women had experienced night sweats compared with 76.3% of Caucasians.³² SWAN data also showed a similar pattern, with Japanese women living in the United States reporting the lowest prevalence of VMS (11.8%, vs 24.2% in Caucasian, 38.8% in African American, 26.0% in Hispanic, and 15.5% in Chinese women).³³ Even after stratifying by menopausal status, the proportion of Japanese women in the United States who reported VMS was lower than in African American, Hispanic, and Caucasian women (in women with VMS for ≥ 6 days at baseline, the prevalence was 3.3% in Japanese women, vs 38.0%, 10.5%, and 43.4% in African American, Hispanic, and Caucasian women, respectively).³

It should be noted, however, that in addition to differences in the ages of the populations studied (age range 42–52 years in SWAN³⁴ and 40–60 years in Japanese studies^{30,31,35}), each study used different questionnaires. Compared with previous studies that enrolled patients ≤ 60 years old,^{28–31,35} the present study provided data for a wider age range of women. Furthermore, many Japanese studies have targeted patients who consulted a menopausal clinic,^{11,35} but these women may differ from the community-dwelling population, for instance, being more likely

to be experiencing VMS. It is important to investigate the general population because not all women experiencing menopausal symptoms will consult a doctor. In this study, only 7.4% of participants reporting hot flashes had or were currently receiving menopausal HT.

Results from studies of Italian and North American women showed that the prevalence of hot flashes was highest among women with lower levels of education.^{36,37} This was also the case for the SWAN study in all groups except for Hispanic women.³ A previous cross-sectional community survey of Japanese women found that high school or college graduates more frequently reported hot flashes and sweats than those with lower levels of education.²⁹ In the present study, highly educated Japanese women were more likely to be prone to menopausal symptoms. However, on examination of the association between hot flashes and education, stratified by age, no significant association was suggested (data not shown).

In the present study population, approximately 20% of women reported hot flashes even after age 60 years and nearly half reported sweating >5 years postmenopause. According to SWAN data, VMS lasted even after the final menopausal period for a median of 4.5 years.³⁴ Women who were premenopausal or early perimenopausal when they first reported frequent VMS had the longest total VMS duration and longest persistence of VMS after the final menstrual period.³⁴

The proportion of women reporting sweating was not typically associated with menopausal transition status in this study population. VMS usually includes night sweats as part of its spectrum of symptoms but in the KCSI the question does not ask if the subject experiences actual sweating during the day or night, but rather if they feel liable to sweating.³⁸

Clear associations were found between hot flashes and sleeping problems, even with an adjustment for potential confounding factors. SWAN and other studies have shown that vasomotor symptoms are strongly associated with poor sleep quality.^{39–41} Additional studies have shown that hot flashes with bother, although not hot flashes alone, are associated with sleep disturbance.⁴² Generally, higher daily activity was associated with longer sleeping hours and urination during the night was associated with shorter (disrupted) sleeping hours.

Poorer psychological outcomes were also associated with hot flashes in the present study. Moderate-to-severe VMS have been found to be independently and

significantly associated with moderate–severe depressive symptoms.¹⁰ When associations between hot flashes and depressed mood were examined in a 10-year follow-up of the Penn Ovarian Aging cohort, among women who had no previous experience of either symptom, 41% reported both hot flashes and depressive symptoms.⁴³

The present study did not find any association between hot flashes and any dietary factors studied, and it is possible that any association between sweating and dietary factors occurred by chance. In contrast, a recent study in 262 women aged 40–65 years concluded that Vitamin B₆ and oily fish intake were inversely associated with the severity of hot flashes.⁴⁴ Furthermore, it is possible that high consumption of soy products, which contain phytoestrogens, may be associated with the lower prevalence of hot flashes.⁴⁵ Indeed, a number of randomized controlled trials report that phytoestrogens reduce the frequency of hot flashes in menopausal women,⁴⁶ and S-equol soy derivative is recommended with caution by the North American Menopause Society (NAMS).⁴⁷

The present study was exploratory and was not designed to elucidate risk factors. Hence, only a few potential confounding factors selected a priori were included in the models. We were not able to comprehensively examine the relationship between new or previously unsuspected or untested variables or covariates. Limitations of the study include the low value of R^2 in the general linear model, the potential for participation bias because only a minority (30%) of those who sent invitation letters actually participated, and also that multiple comparisons could have resulted in chance findings of statistical significance. Also, the relatively small number of women with hot flashes could have resulted in inadequate statistical power to identify meaningful differences as statistically significant. A further limitation of this study is that because of the cross-sectional nature of the data, a causal relationship between VMS and sleep problems, psychological outcomes, or nutrition could not be established. VMS and sleeping problems are known to be bi-directional: in addition to being a consequence of VMS, sleep problems can influence the extent to which VMS are bothersome. In order to analyze the causal relationship between hot flashes and the outcomes, or hot flashes as an outcome (i.e., sleeping, psychological, or dietary factors as preventive or risk factor of hot flashes), longitudinal data analysis is required. Furthermore, the present study did not examine passive smoking, anxiety symptoms, stress, or history of premenstrual symptoms, although

these have all been reported to be associated with VMS.⁴⁸ In addition, VMS in this study was defined as a response to the KKSI, where the severity was determined by self-reporting, not by number of hot flashes/day or per week. A further limitation is that the present study did not take into account the symptom of chilliness, which is considered to be a more important VMS than hot flashes and sweats in Japanese women and may reflect differing thermoregulatory physiology.⁴⁹

In conclusion, in this community-dwelling study population of women with a typical Japanese lifestyle, prevalence of hot flashes was 24.5%, and was highest in the 50–54 year age group (45.2%) or 2–5 years post-menopause (47.7%). Severity of hot flashes was also highest in the 50–54 year age group. The proportion of women reporting sweating was not typically associated with menopausal transition status in this study population. Clear associations were found between hot flashes and sleeping problems, even after adjusting for potential confounding factors. Women reporting hot flashes were more likely to be at risk of having depressive symptoms and had lower life satisfaction, self-esteem, and self-rated health status compared with those without hot flashes. No association between hot flashes and dietary factors was found.

Data sharing statement

Researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellas-sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: <https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx>. The data that support the findings of this study are available from the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the NILS-LSA.

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Conflict of Interest

Makiko Tomida, Rei Otsuka, Chikako Tange, Yukiko Nishita, and Hiroshi Shimokata report (F) research funding from Astellas Pharma Inc. Tomomi Kimura, Matthias Stoelzel, and Keiko Tanaka-Amino are (A) employees of Astellas Pharma. Masakazu Terauchi reports (F) grants from Kikkoman Corporation and Ibaraki Prefecture, and (G) personal fees from Fuji Pharma Co. Ltd., personal fees from Bayer Holding Ltd., and personal fees from Hisamitsu Pharmaceutical Co., Inc.

Author contributions

All authors made a substantial contribution to the study design and interpretation of the study data. MT, RO, CT and YN were responsible for the acquisition of study data. MT and TK conducted the analyses of the study data. All authors also contributed to writing the manuscript and approved it for submission.

Data Availability Statement

Researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: <https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx>. The data that support the findings of this study are available from the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the NILS-LSA.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Distribution of age at menopause.

Table S1 Prevalence of other KCSI symptoms in women with/without hot flashes and sweating, *n* (%)

Table S2 Sleeping time in women with/without hot flashes and sweating (unadjusted and adjusted results)

Table S3 Psychological outcomes by severity of hot flashes (adjusted results)

Table S4 Dietary intake in women (a) with/without hot flashes and (b) with/without sweating