https://doi.org/10.5664/jcsm.9180

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Hot-water bathing before bedtime and shorter sleep onset latency are accompanied by a higher distal-proximal skin temperature gradient in older adults

Yoshiaki Tai, MD, PhD[1,2]; Kenji Obayashi, MD, PhD[1]; Yuki Yamagami, RN, PHN, PhD[1]; Kiyomi Yoshimoto, MD, PhD[2]; Norio Kurumatani, MD, PhD[1]; Kenji Nishio, MD, PhD[2]; Keigo Saeki, MD, PhD[1]

[1]Department of Epidemiology, Nara Medical University School of Medicine, Nara, Japan; [2]Department of General Medicine, Nara Medical University School of Medicine, Nara, Japan

Study Objectives: Passive body heating in controlled settings could shorten sleep onset latency (SOL). The hypothesized mechanism is vasodilation-induced heat loss before bedtime. However, this evidence is based on small sample–sized studies in specific populations. Thus, we analyzed the association of hot-water bathing and its before-bedtime timing with SOL and heat loss in a large study population of older adults.

Methods: We conducted a longitudinal analysis using repeated measurements of hot-water bathing and sleep among 1,094 older adults (mean age, 72.0 years). SOL was recorded using actigraphy and self-reported sleep estimates and was categorized into conditions (intervals of 1–60, 61–120, 121–180, and > 181 minutes between hot bath and bedtime) and compared with the control condition of no bathing. The heat-loss indicator, distal-proximal skin temperature gradient, was examined in the same categorization.

Results: Mixed-effects linear regression models suggested that the bathing conditions of 61–120 minutes and 121–180 minutes showed significantly shorter log-transformed actigraphic SOL by 0.23 log-minutes (95% confidence interval (CI), 0.03–0.42) and 0.32 log-minutes (95% CI, 0.09–0.56), shorter self-reported SOL by 0.16 log-minutes (95% CI, 0.02–0.30) and 0.18 log-minutes (95% CI, 0.01–0.35), and higher distal-proximal skin temperature gradient for 30 minutes before bedtime by 0.49°C (95% CI, 0.22–0.75) and 0.51°C (95% CI, 0.20–0.83), respectively, independent of potential confounders.

Conclusions: Hot-water bathing before bedtime is significantly associated with shorter SOL and higher distal-proximal skin temperature gradient among the large-scale older population. This finding could enhance the generalizability of hot-water bathing habits for ameliorating sleep initiation difficulty.

Keywords: actigraphy, skin temperature, older adults, passive body heating

Citation: Tai Y, Obayashi K, Yamagami Y, et al. Hot-water bathing before bedtime and shorter sleep onset latency are accompanied by a higher distal-proximal skin temperature gradient in older adults. *J Clin Sleep Med*. 2021;17(6):1257–1266.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Previous laboratory studies have shown that passive body heating could accelerate sleep initiation. However, it is uncertain whether hot bathing in home settings is associated with an acceleration of sleep initiation and whether a large-scale study would demonstrate the same trend.

Study Impact: We showed that hot-water bathing was associated with acceleration of sleep initiation, particularly when bathing was scheduled 1–3 hours before bedtime, independent of age, sex, body mass index, income, sleep medication use, physical activity, bedtime, and indoor temperature. Our findings could expand the generalizability of passive body heating among older adults as a habit to ameliorate sleep initiation difficulty, which is a risk factor for cardiovascular disease, depression, dementia, and all-cause mortality.

INTRODUCTION

With age, sleep initiation and maintenance are impaired, and altered sleep physiology may underlie these disturbances in older adults. An epidemiologic study estimated that over half of adults ≥ 65 years had insomnia symptoms and 10%–25% complained about difficulty in initiating sleep.[1] Difficulty initiating sleep has been associated with an increased risk of a vast range of conditions, including diabetes,[2] metabolic syndrome,[3] cardiovascular disease,[4–6] depression,[7] dementia,[8] and all-cause mortality.[9] A nonpharmacological intervention for sleep problems in older adults with no or limited adverse effects is preferred to pharmacological interventions with known adverse effects, such as excessive sedation, cognitive impairment,[10] falls,[11] and impaired performance of daily activities.[12]

Thermoregulatory processes are associated with sleep initiation.[13] Skin temperature increases prior to the onset of sleep. The degree of vasodilation in the distal skin regions, which increases heat loss at extremities, is associated with reduced sleep onset latency (SOL).[14] The distal-proximal skin temperature gradient (DPG) is an indirect measure of heat loss in the distal skin region. Selective vasodilation of distal skin regions manipulated by bright light, a meal, or melatonin can shorten SOL,[15] and the reverse is also true; patients with vasospastic syndrome have prolonged SOL.[16] Additionally, passive body heating (PBH) could shorten SOL

by elevating core body temperature (CBT) and triggering subsequent heat loss.[17] Further, skin temperature manipulation, even within the normal range of nocturnal fluctuation, is reported to modulate SOL. It is hypothesized that elevated skin temperature without CBT changes may shorten SOL by providing a signal to thermosensitive neurons that play a key role in sleep-awake regulation.[18,19]

A recent meta-analysis (n = 294), including young adults, suggested that water-based PBH was associated with shortening of SOL by a standardized mean difference (Cohen's *d*) of 1.01 compared with baseline measurements when scheduled 1–2 hours before bedtime and conducted for at least 10 minutes.[20] Japanese individuals follow a custom of soaking themselves in hot water baths in the evenings. Japanese-style bathing at home is also expected to improve difficulty in initiating sleep. However, there is still uncertainty regarding the ecological validity of the effect of water-based PBH on SOL. To our knowledge, previous studies were limited to relatively small sample sizes, specific populations, and controlled laboratory settings, relative to fixed timing, temperature, and duration of PBH recordings. Although 2 randomized controlled trials investigated the effect of PBH on SOL among patients with traumatic brain injury (n = 23) and older men (n = 46), both trials examined only the impact of foot baths.[21,22] Small sample size could lead to residual confounding and inaccurate estimation even in a randomized controlled study due to higher measurement variability and bias introduction in the data. Besides, the previous report suggested that Japanese-style bathing before bedtime in real life could occur under varying behaviors with respect to timing and environmental conditions.[23]

We sought to evaluate the association between hot-water bathing, at varying time intervals preceding bedtime, and SOL among the older general population. We conducted a longitudinal analysis using repeated measurements of hot-water bathing (varying time intervals) before bedtime and SOL among 1,094 home-dwelling older adults. In addition, to identify the optimal bathing conditions for shortening SOL, we evaluated different combinations of bath duration and time elapsed between bathing and going to bed. In a subgroup of participants (n = 569), DPGs were compared according to bathing conditions to investigate whether hot-water bathing before bedtime was associated with heat loss in distal skin regions at the time of sleep initiation.

METHODS

Participants and study protocol

This longitudinal analysis of repeated measurements of hot-water bathing and subsequent sleep was performed on baseline data from a community-based cohort study: the Housing Environments and Health Investigation among Japanese Older People in Nara, Kansai Region (HEIJO-KYO) study.[24] We recruited a total of 1,127 volunteers aged at least 60 years between September 2010 and April 2014. Of these, we completed measurements during the colder months (October to April) in 1,122 participants. We excluded 10 participants who only showered, 3 participants who did not complete their bathing diaries, and 15 participants without data on actigraphic SOL. Consequently, our study included 1,094 participants in the analysis (**Table 1**). All participants provided written informed consent. The study protocol was reported in a previous study and approved by the Nara Medical University ethics committee (No. 301).[24,25] In summary, we visited each participant's house and acquired demographic and medical information using a standardized questionnaire. Subsequently, we placed temperature loggers in multiple places in the home and attached an accelerometer on each participant's wrist. We then measured the indoor temperature and physical activity for a consecutive 48 hours (from noon on the first day to noon on the third day). We tracked sleep and bathing behaviors by instructing participants to keep a standardized diary during the same period.

Self-reported and actigraphic SOL

Self-reported SOL was determined according to the diary log of bedtime and clock time for falling asleep for 2 nights. We measured sleep onset by actigraph based on bedtime recordings in the diary and physical activity. Physical activity was measured at 1-minute intervals using the actigraph (Actiwatch 2; Respironics Inc., Murrysville, PA) worn on the nondominant wrist for a consecutive 48 hours. Data were analyzed using Actiware (version 5.5; Respironics Inc.). Sleep onset was defined as the first minute followed by a 10-minute immobility period that contained no epoch with any motion. Actigraphic SOL was the time from bedtime to the actigraphic sleep onset.

Bathing behavior and environment

Behavioral information about bathing was determined using the diary for bathing start time, bathing end time, time of soaking in the bathtub (bathing duration), bedtime, and the time interval between bathing end and bedtime (time before bedtime). Water temperature in the bathtub was measured using the Thermochron iButton DS1992L (Maxim Integrated, Dallas, TX), which had a measurement accuracy, range, and resolution of ± 0.5°C, −10 to +65°C, and 0.0624°C, respectively, at 1-minute intervals for 48 hours in the same position without changing the measurement conditions. Temperatures of the bathroom, dressing room, bedroom, and living room were measured 60 cm above the floor at 10-minute intervals for 48 hours. We calculated the mean water temperature in the bathtub (water temperature) and the mean temperature of the bathroom and dressing room in the time between bathing start and bathing end. Evening indoor temperature was defined as the mean temperature measured for 2 hours before bedtime at the participants' home. Whether the participants were in their living room or bedroom was determined according to the diaries. Outdoor temperatures at 10-minute intervals were provided from the local meteorological office in Nara prefecture (latitude of 34 degrees north).

To compare bathing conditions with no bath control, we classified bathing duration and time before bedtime according to thresholds as previously described.[20] A previously reported meta-analysis of experimental studies showed that before bedtime, PBH for ≥ 10 minutes significantly shortened SOL when participants scheduled a bath 1–2 hours before bedtime. Based on this information, all bathing sessions were divided into

Table 1—Basic and clinical characteristics of participants (n = 1,094).

	Days of Taking a Hot Bath in 2-Day Survey			*P* Trend
	Neither (n = 76)	Either Day (n = 255)	Both Days (n = 763)	
Demographic parameters				
Age, mean (SD), y	76.2 (7.5)	74.1 (6.4)	70.8 (7.0)	< .001
Sex, male	37 (48.7%)	115 (45.1%)	360 (47.2%)	.883
Body mass index, mean (SD), kg/m^2	22.2 (3.2)	23.0 (3.0)	23.2 (3.1)	.022
Current smoker	7 (9.2%)	14 (5.5%)	35 (4.6%)	.110
Alcohol consumption (≥ 30 g/d)	7 (9.2%)	34 (13.3%)	112 (14.7%)	.204
Household income (≥ 4 million JPY/y)	13 (18.6%)	81 (34.2%)	702 (47.9%)	< .001
Past education (≥ 13 y)	15 (19.7%)	65 (25.5%)	211 (26.6%)	.138
History of night-shift work	7 (10.3%)	14 (6.1%)	52 (7.3%)	.746
Clinical parameters				
Antihypertensive medication use	30 (39.5%)	125 (49.0%)	333 (43.6%)	.731
eGFR, mean (SD), mL/min/1.73 m^2	73.5 (18.3)	71.1 (15.5)	72.5 (14.8)	.351
Sleep medication use	9 (11.8%)	30 (11.8%)	76 (10.0%)	.398
Antidepressant use	1 (1.3%)	6 (2.4%)	8 (1.0%)	.309
Daytime physical activity,* mean, count	264.6 (106.5)	277.6 (101.7)	308.0 (101.4)	< .001
Bedtime,* mean (SD), clock time	21:52 (1:15)	22:20 (1:14)	22:36 (1:07)	< .001
Rising time,* mean (SD), clock time	6:49 (1:08)	6:53 (0:58)	6:46 (0:53)	.193
Self-reported SOL,* median (IQR), min	26.5 (13.1–61.9)	30.0 (15.5–71.0)	28.0 (15.0–52.3)	.044
Mean (SD), log-min	3.38 (0.93)	3.47 (0.93)	3.28 (0.88)	.016
Actigraphic SOL,* median (IQR), min	22.5 (9.6–55.9)	20.5 (10.0–40.5)	17.5 (9.0–33.3)	.006
Mean (SD), log-min	2.83 (1.25)	2.82 (1.07)	2.69 (0.94)	.118

P trend was calculated using linear regression, logistic regression, and Jonckheere-Terpstra test. *Means of days 1 and 2. eGFR = estimated glomerular filtration rate, IQR = interquartile range, JPY = Japanese yen, SD = standard deviation, SOL = sleep onset latency.

bathing duration < 10 minutes and bathing duration ≥ 10 minutes. Furthermore, data of bathing duration ≥ 10 minutes were classified into intervals of 1–60 minutes, 61–120 minutes, 121–180 minutes, and ≥ 181 minutes between the end of bathing and bedtime.

Skin temperature

We measured skin temperature of 569 participants enrolled in this study on or after October 24, 2012. Proximal (abdomen) and distal (mean of wrist and ankle) skin temperatures were measured at 1-minute intervals using the same device for a consecutive 48 hours. We attached the device to the right upper quadrant of the abdominal skin with Tegaderm transparent dressing (3M, St. Paul, MN). The iButtons were attached to a silicone band with adjustable diameter that we then applied to the flexor surface of the dominant wrist (the opposite side of the actigraph) and to the lateral flat surface of the ankle. We instructed participants not to detach the bands for a consecutive 48 hours. We did not cover the silicone band or Tegaderm transparent dressing. Proximal skin temperature measurement of < 25°C and distal skin temperature measurement of < 20°C were excluded from the analysis as measurement error. DPG was calculated as distal skin temperature minus proximal skin temperature, and it was an indirect measure of blood flow as well as heat loss in the distal skin region.[14,26] We calculated mean DPG for 30 minutes after participants went to bed as an average of a series of subsequent readings to detect heat loss shortly after getting in bed and mean DPG for 30 minutes before the bathing start time, in the same way, to detect heat loss before PBH. For the days without bathing, mean DPG corresponding to 30 minutes before bathing was calculated as mean DPG for 30 minutes before the median bathing start time of "bathing days."

Other measurements

Smoking and drinking habits, household income, educational qualifications, work-shift history, medication use, and medical history were recorded during an interview to enable adjustment for confounding factors in analysis of associations. The estimated glomerular filtration rates (eGFR) were calculated using the formula that follows, which was published in the Japanese Society of Nephrology– Evidence-based Practice Guideline for the Treatment of CKD:[27] eGFR (mL/min per 1.73 m^2) = 194 × [serum creatinine (mg/dL)]$^{-1.094}$ × [age (years)]$^{-0.287}$ × [sex]. For females and males, the values were 0.739 and 1.000, respectively. Self-reported sleep quality over a 1-month time interval was assessed using the Pittsburgh Sleep Quality Index, which measures 7 areas: self-reported sleep quality, latency, duration, efficiency, and disturbances, along with daytime dysfunction and use of sleep medication. Each component was scored on a scale of 0–3. The global score was calculated by a total of the 7-component score.[28] A global score of ≥ 6 was used for detecting sleep disturbance.

Statistical analyses

Normally distributed continuous variables were expressed as mean and standard deviation; nonnormally distributed variables were reported as median (interquartile range, [IQR]). Mean values were compared utilizing unpaired *t* tests and 1-way analysis of variance. Median values were analyzed using the Mann-Whitney *U* test, Kruskal-Wallis test, and Steel-Dwass test. Trends in acquired data were evaluated using linear regression, logistic regression, and the Jonckheere-Terpstra trend test. To evaluate the interdependency of bathing conditions, SOL, and DPG within participants, we calculated the intraclass correlation coefficient using a 1-way random model.

Median of SOL for each of the 5 categories of bathing conditions described previously was compared to median without hot-water bathing using all data irrespective of the first or second night. Sensitivity analyses of SOL with varying bathing duration were performed, and data of bathing duration ≥ 1, 5, and 15 minutes were also sorted into intervals of 1–60 minutes, 61–120 minutes, 121–180 minutes, and ≥ 181 minutes between the end of bathing and bedtime.

We evaluated the association of each bathing condition with log-transformed SOL using a linear mixed-effect regression model consisting of participant-level variables (age, sex, body mass index [BMI], smoking and drinking status, household income, educational qualifications, work-shift history, use of sleep medication, use of antidepressants, use of antihypertensive medication, and eGFR) and measurement of day-level variables (bathing conditions, bedtime, evening indoor temperature, and daytime physical activity). We also evaluated the association of each bathing condition with DPG and the association between DPG and log-transformed SOL using a linear mixed-effect regression model adjusted for age and sex. We considered the measurements of bathing conditions, DPG, and SOL to be nested within each participant in a linear mixed-effect regression. The bathing conditions were expressed as 5 dummy variables according to the 5 previously described categories. Differences in SOLs between the control and each bathing condition were derived from regression coefficients of the dummy variables using a linear mixed-effect regression, representing the following equation with a subscript for measurement-days (i) and participants (j). Measurement of day-level: log-transformed $SOL_{ij} = \beta_{0j} + \beta_1 \times dummy1 + \beta_2 \times dummy2 + \beta_3 \times dummy3 + \beta_4 \times dummy4 + \beta_5 \times dummy5 + \beta_6 \times bedtime + \beta_7 \times evening\ indoor\ temperature + \beta_8 \times daytime\ physical\ activity + \varepsilon_{ij}$. Participant-level; $\beta_{0j} = \gamma_{00} + \gamma_{01} \times age + \gamma_{02} \times sex + \gamma_{03} \times BMI + \gamma_{04} \times smoking\ status + \gamma_{05} \times drinking\ status + \gamma_{06} \times income + \gamma_{07} \times educational\ qualifications + \gamma_{09} \times work\text{-}shift\ history + \gamma_{010} \times sleep\ medication\ use + \gamma_{011} \times antidepressants\ use + \gamma_{012} \times antihypertensive\ use + \gamma_{013} \times eGFR + u_{0j}$, where β_{0j} is the means of intercept for the j^{th} participant; γ_{00} is the participant-level intercept; ε_{ij} and u_{0j} represent measurement of day-level and participant-level random effects, respectively; and dummy1–5 represent dummy variables of the 5 bathing conditions. Regression coefficients were estimated by maximum likelihood.

The Steel-Dwass test was performed using EZR 1.36 for Windows (Jichi Medical University, Shimotsuke, Japan).[29] The other analyses were performed using SPSS 26.0 for Windows (IBM SPSS Inc., Chicago, IL). All test distributions were 2-sided, and a P value < .05 was considered statistically significant.

RESULTS

Among the 1,094 participants, 1,045 completed the consecutive 48-hour session, 29 completed only the first 24-hour session, and 20 completed only the last 24-hour session. We analyzed a total of 2,139 nights (1,781 nights bathing and 358 nights not bathing). The mean age of all 1,094 participants was 72.0 years (standard deviation, 7.1 years), and 512 participants (46.7%) were male. The median age was 72 years (IQR, 66–77). The mean bedtime was 22:30 (standard deviation, 1:11). Median actigraphic and self-reported SOL was 18.5 minutes (IQR, 9.5 –35.5) and 29.0 minutes (IQR, 15.0–55.0), respectively. Sleep disturbance with a Pittsburgh Sleep Quality Index score ≥ 6 was found in 383 participants (35.0%). The number of participants who took medication for insomnia, depression, hypertension, and diabetes was 115 (10.5%), 15 (1.4%), 488 (44.6%), and 102 (9.3%), respectively.

For our 2-day measurements, among the 1,094 participants, 763 took a hot bath on both days of measurement, 255 took a hot bath on day 1 or 2, and 76 did not take a hot bath on either day. Bathing for both days during the 2-day survey was significantly associated with increased BMI, household income, daytime physical activity, bedtime, decreased age, actigraphic, and self-reported SOL. A prolonged time interval between bathing and bedtime was significantly associated with earlier bathing, higher water temperature, and higher dressing room temperature (**Table 2**). Day-to-day correlation of log-transformed time before bedtime, bathing duration, water temperature, log-transformed self-reported/actigraphic SOL, and mean DPG for 30 minutes before going to bed and for 30 minutes after going to bed was 0.70 (95% confidence interval [CI], 0.66–0.73), 0.76 (95% CI, 0.73–0.79), 0.69 (95% CI, 0.64–0.72), 0.55 (95% CI, 0.50–0.59)/0.26 (95% CI, 0.21–0.32), 0.53 (95% CI, 0.47–0.58), and 0.52 (95% CI, 0.45–0.59), respectively.

Self-reported SOL was significantly shorter in hot bathing 61–120 minutes before bedtime (median: 25 minutes, IQR: 10–45, P = .005) and hot bathing 121–180 minutes before bedtime (median: 24 minutes, IQR: 14–40, P = .021) compared with not bathing (median: 30 minutes, IQR: 15–60) (**Table 3**). Hot bathing 61–120 minutes, 121–180 minutes, and ≥ 181 minutes before bedtime showed a significantly shorter log-transformed self-reported SOL by 0.18 (95% CI, 0.06–0.31), 0.18 (95% CI, 0.03–0.33), and 0.17 (95% CI, 0.02–0.33) log-minutes, respectively, compared with not bathing (**Table 3**). The difference remained significant in hot bathing 61–120 minutes and 121–180 minutes before bedtime when adjusted for participant-level variables (age, sex, BMI, smoking and drinking habits, household income, educational qualifications, work-shift history, use of sleep medication, use of antidepressants, use of antihypertensive medication, and eGFR). Hot bathing for 61–120 minutes and 121–180 minutes before

Table 2—Bathing and sleep parameters according to time before bedtime.

	Time Before Bedtime (min)				*P* Trend
	1–60	61–120	121–180	≥ 181	
Number of nights	803	467	261	250	
Time					
Bathing start, mean	21:38 (1:17)	20:39 (1:13)	19:35 (1:15)	18:00 (1:17)	< .001
Bathing end, mean	22:05 (1:17)	21:06 (1:13)	20:02 (1:15)	18:28 (1:15)	< .001
Bedtime, mean	22:34 (1:15)	22:35 (1:11)	22:29 (1:12)	22:41 (1:02)	.594
Rising time, mean	6:49 (0:58)	6:40 (0:56)	6:48 (0:59)	6:48 (0:53)	.654
Bathing duration, median, min	11 (9–16)	13 (11–16)	11 (9–16)	13 (9–16)	.838
Time before bedtime, median, min	29 (15–41)	90 (73–103)	146 (135–161)	240 (205–284)	< .001
Temperature, mean, °C					
Water temperature*	40.7 (1.3)	40.8 (1.3)	40.8 (1.4)	40.9 (1.4)	.036
Bathroom*	16.2 (4.4)	16.5 (4.3)	16.5 (4.5)	16.5 (4.3)	.252
Dressing room*	13.3 (4.1)	13.5 (4.2)	13.4 (3.9)	13.9 (4.0)	.045
Indoor†	16.8 (3.9)	17.0 (3.8)	16.7 (4.0)	16.7 (3.9)	.071
Outdoor†	6.5 (4.9)	6.6 (4.9)	6.3 (4.9)	6.1 (5.0)	.261

Data are expressed as means with standard deviation and medians with interquartile range. Unpaired *t* test and Mann-Whitney *U* test were used to compare means and medians. *P* trend was calculated using linear regression and Jonckheere-Terpstra test. *Mean temperature during bathing. †Mean temperature for 2 hours before bedtime. Bathing duration = time of soaking in the bathtub, Time before bedtime = time interval between bathing end and bedtime, Water temperature = temperature of hot water in the bathtub.

Table 3—Self-reported and actigraphic sleep onset latency stratified by bathing conditions.

	Control	Bath				
		Bathing Duration < 10 min	Bathing Duration ≥ 10 min			
			Time Before Bedtime (min)			
			1–60	61–120	121–180	≥ 181
Self-reported SOL, median (IQR), min	30 (15–60)	25 (13.5–55)	25 (15–55)	25 (10–45)	24 (14–40)	25 (10–54)
Number of nights	348	436	587	353	181	180
P value*	—	.250	.205	.005	.021	.094
Actigraphic SOL, median (IQR), min	18 (7–41)	17 (7–37)	18 (8–35)	13.5 (5–30)	12 (4–26)	15 (6–35)
Number of nights	358	445	602	362	187	185
P value*	—	.989	.999	.021	.004	.557

*SOL in the control condition was compared with 5 bathing conditions. *P* values were calculated using the Steel-Dwass test. Bathing Duration = time of soaking in the bathtub, IQR = interquartile range, SOL = sleep onset latency, Time Before Bedtime = time interval between bathing end and bedtime.

bedtime showed an adjusted difference of −0.19 log-minutes (95% CI, −0.33 to −0.06, $P = .006$) and an adjusted difference of −0.21 log-minutes (95% CI, −0.32 to −0.04, $P = .014$), respectively. The same was true after adjustment for participant-level variables and measurement of day-level variables (bedtime, daytime physical activity, and evening indoor temperature) (adjusted model, **Table 4**). These differences derived from the estimated coefficients were back-transformed from 0.16 and 0.18 log-minutes (in adjusted model, **Table 4**) to a 14.8% and 16.5% reduction of self-reported SOL from the control, using the following calculation: $e^{-0.16} = 0.852$ (85.2%) and $e^{-0.18} = 0.835$ (83.5%), where e is Euler's number.

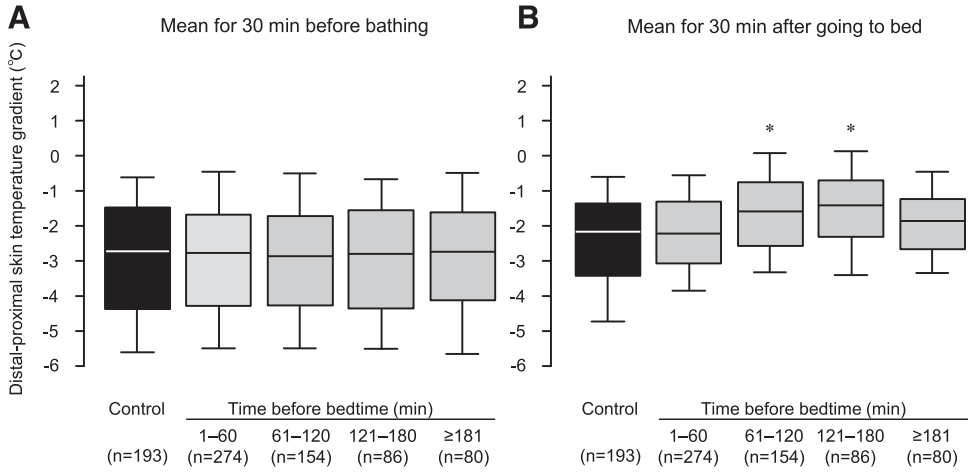
Consistently, actigraphic SOL was significantly shorter in hot bathing 61–120 minutes before bedtime (median: 13.5 minutes, IQR: 5–30, $P = .021$) and 121–180 minutes before bedtime (median: 12 minutes, IQR: 4–26, $P = .004$), compared with the control condition (median: 18 minutes, IQR: 7–41, **Table 3**). Similarly, hot bathing 61–120 minutes and 121–180 minutes before bedtime showed significantly shorter log-transformed actigraphic SOL by 0.21 log-minutes (95% CI, 0.03–0.38) and 0.32 log-minutes (95% CI, 0.10–0.53), respectively, compared to not bathing (**Table 4**). Multivariable models adjusted for the all participant-level variables revealed significantly shorter actigraphic SOL in hot bathing 61–120 minutes before bedtime by 0.24 log-minutes (95% CI, 0.05–0.43, $P = .015$) and in hot bathing 121–180 minutes before bedtime by 0.34 log-minutes (95% CI, 0.10–0.57, $P = .005$), respectively. The difference remained significant in hot bathing 61–120 minutes and 121–180 minutes before bedtime when adjusted for participant-level variables and

Table 4—Linear mixed-effect model analysis of the unadjusted and adjusted association of bathing conditions with log-transformed sleep onset latency.

	Control	Bath				
		Bathing Duration < 10 min	Bathing Duration ≥ 10 min			
			Time Before Bedtime (min)			
			1–60	61–120	121–180	≥ 181
Self-reported SOL						
Number of participants*	298	296	422	290	161	141
Crude difference (95% CI), log-min	Ref	−0.05 (−0.18 to 0.07)	−0.11 (−0.22 to 0.01)	−0.18 (−0.31 to −0.06)	−0.18 (−0.33 to −0.03)	−0.17 (−0.33 to 0.02)
P value	—	.396	.066	.004	.020	.030
Adjusted difference (95% CI), log-min†	Ref	0.03 (−0.11 to 0.17)	−0.07 (−0.19 to 0.06)	−0.16 (−0.30 to −0.02)	−0.18 (−0.35 to −0.01)	−0.14 (−0.31 to 0.04)
P value	—	.695	.310	.022	.033	.123
Actigraphic SOL						
Number of participants*	298	297	422	290	162	141
Crude difference (95% CI), log-min	Ref	0.03 (−0.14 to 0.20)	0.06 (−0.10 to 0.22)	−0.21 (−0.38 to −0.03)	−0.32 (−0.53 to −0.10)	−0.12 (−0.34 to 0.09)
P value	—	.739	.459	.024	.004	0.262
Adjusted difference (95% CI), log-min†	Ref	0.11 (−0.08 to 0.30)	0.13 (−0.05 to 0.31)	−0.23 (−0.42 to −0.03)	−0.32 (−0.56 to −0.09)	−0.16 (−0.40 to 0.08)
P value	—	0.273	0.155	0.024	0.007	0.186

Differences in SOLs were derived from regression coefficients on the dummy variables using the mixed-effect linear regression model. *The sum of the number of participants exceeds the total participants (n = 1,094) because a participant who had 1 night in 1 bathing category and the other night in another bathing category was counted twice. †Adjusted for age, sex, body mass index, smoking and drinking status, income, past education, shift work, sleep medication use, antidepressant use, antihypertensive medication use, eGFR, bedtime, physical activity, and indoor temperature. Bathing Duration = time of soaking in the bathtub, CI = confidence interval, eGFR = estimated glomerular filtration rate, Ref = reference, SOL = sleep onset latency, Time Before Bedtime = time interval between bathing end and bedtime.

Figure 1—Box plots of DPGs according to time intervals between bathing and bedtime.



DPGs were calculated as distal skin temperature (mean of wrist and ankle) minus proximal (abdomen) skin temperature. Mean DPG for 30 minutes before bathing or corresponding clock time **(A)** and mean DPG for 30 minutes after going to bed **(B)** are presented as medians and 25th and 75th percentiles (boxes) and 10th and 90th percentiles (whiskers), respectively. Mean DPG of the control condition was compared with those of the 4 time-before-bedtime conditions using Dunnett's test. *$P < .001$ was considered significant. DPGs = distal-proximal skin temperature gradients, Time before bedtime = time interval between bathing end and bedtime.

measurement of day-level variables (adjusted model, **Table 4**). These differences derived from the estimated coefficients were back-transformed from 0.23 and 0.32 log-minutes (in adjusted model, **Table 4**) to a 20.6% and 27.4% reduction of actigraphic SOL from the control, using the following calculation: $e^{-0.23} = 0.794$ (79.4%) and $e^{-0.32} = 0.726$ (72.6%).

In the sensitivity analyses of SOL, when hot-water bathing duration under bathing duration condition varied ≥ 1, 5, and 15

minutes, the significant association between SOL and bathing conditions remained largely consistent (**Table S1** in the supplemental material).

There were no significant differences between the hot bathing conditions and the not bathing condition in the mean DPG for 30 minutes before bathing or for corresponding clock time (**Figure 1A**). However, the mean DPG for 30 minutes after going to bed was significantly higher among the hot bathing conditions, with hot bathing 61–120-minute and 121–180-minute conditions values of 0.66°C (95% CI, 0.27–1.06, $P < .001$) and 0.79°C (95% CI, 0.31–1.26, $P < .001$), respectively, compared with the control condition (**Figure 1B**). In mixed-effect linear regression models adjusted for age and sex, hot bathing 61–120 and 121–180 minutes before bedtime showed significantly higher mean DPG for 30 minutes after going to bed by 0.49°C (95% CI, 0.22–0.75, $P < .001$) and 0.51°C (95% CI, 0.20–0.83, $P = .001$), respectively, compared with the control condition. Mixed-effects linear regression models adjusted for age and sex showed that a 1°C increase in DPG was significantly associated with a 0.05-log-minute (95% CI, 0.01–0.09, $P = .008$) decrease in self-reported SOL and a 0.14-log-minute (95% CI, 0.08–0.19, $P < .001$) decrease in actigraphic SOL, respectively.

In subanalysis excluding participants whose Pittsburgh Sleep Quality Index score was ≥ 6 and those using sleep medication, 681 participants were included. These 681 individuals showed a consistently significant association of hot bathing 61–120 minutes and 121–180 minutes before bedtime with self-reported and actigraphic SOL. In an adjusted model including all participant- and day-level variables, except for sleep medication use, hot bathing 61–120 minutes and 121–180 minutes before bedtime showed significantly shorter log-transformed self-reported SOL by 0.27 log-minutes (95% CI, 0.09–0.45, $P = .003$) and 0.22 log-minutes (95% CI, 0.004–0.44, $P = .046$), respectively, and shorter log-transformed actigraphic SOL by 0.25 log-minutes (95% CI, 0.001–0.49, $P = .049$) and 0.40 log-minutes (95% CI, 0.11–0.70, $P = .008$), respectively, compared with not bathing.

DISCUSSION

Our results showed that hot-water bathing before bedtime at home was significantly associated with shorter actigraphic and self-reported SOL in a large population of older adults independent of potential confounders including age, sex, BMI, household income, use of sleep medication, bedtime, and physical activity. Significant associations were observed with a hot bath 61–120 or 121–181 minutes before bedtime, which increased with a bathing duration in the following order: ≥ 1, ≥ 5, and ≥ 10 minutes Although comparison of medians can cause the underestimation of P value because the measurements are treated as independent (**Table 3**), the significant associations were consistent with those of the multivariable analysis considering the measurements as nested within participants (**Table 4**). Thus, we showed a wider range of time intervals before bedtime and bathing duration than previously reported.[20] Additionally, the bathing conditions associated with shorter SOL were accompanied by significantly higher DPG measured shortly after bedtime, compared to not bathing. Higher DPG was significantly associated with shorter SOL. To our knowledge, this is the first study suggesting a significant association between hot-water bathing at home before bedtime and shorter SOL accompanied by DPG changes in a large population of older adults.

This population-based study, in real life, is likely to enhance the generalizability of the evidence from the laboratory-controlled study due to the relatively large sample size and investigation of a broader range of bathing conditions. Our present study included actigraphic and self-reported SOL measurements among more than 1,000 participants in the older general population, which permitted comparison of various bathing conditions, adjustment for potential confounders, and performance from a broader perspective. A meta-analysis in a previous study suggested that the optimal timing of PBH for shortening SOL was 1–2 hours before bedtime,[20] but this finding was based on data from 23 patients with vascular dementia and 13 patients with traumatic brain injury from 2 studies, and the duration of PBH was fixed for 30 minutes in both studies.[22,30] Regarding Japanese-style bathing, our report showed that the mean duration of body heating was 13.3 minutes (standard deviation, 5.7), which was comparatively shorter than the duration in the 2 studies.[23] The sensitivity analysis of the present study showed the bathing durations of ≥ 1, ≥ 5, and ≥ 15 minutes scheduled 1–3 hours before bedtime were significantly associated with shorter SOL. Although previous cross-sectional analysis from a self-administered questionnaire from 24,686 adults, a study population larger than our reports, suggested that "having a hot bath" showed negative association with excessive daytime sleepiness,[31] the association between hot-water bathing and SOL was not reported.

A potential mechanism for the acceleration in sleep initiation by hot-water bathing, a kind of PBH, before bedtime is the steep decline in CBT by heat loss after PBH-induced distal skin vasodilation, which mimics the decline in CBT seen during the time preceding habitual bedtime, because habitual sleep onset closely follows the maximum rate of CBT decline in the evening.[32,33] Previous laboratory studies on thermoregulatory manipulation by bright light, a meal, or melatonin showed that the DPG (an index of heat loss and blood flow in distal skin regions that is regulated by arteriovenous anastomoses) during the 1.5 hours before lights-off for bedtime was the best physiologic predictor for sleep initiation and that selective vasodilation of distal skin regions by these manipulations could shorten SOL.[14,15] Conversely, patients with primary vasospastic syndrome have longer SOL than healthy control patients.[16] In addition, women with both vasospastic syndrome and sleep-onset insomnia showed phase delay of dim light-melatonin onset, CBT, and DPG.[34] In this study, the bath timing leading to shorter SOL, a hot bath 1–3 hours before bedtime, was significantly associated with higher mean DPG for 30 minutes after bedtime. Additionally, mean DPG for 30 minutes after bedtime was directly associated with shorter SOL. The observed increase in DPG with these bathing conditions was considered to be in line with the delayed heat loss process as a mechanism for accelerating sleep initiation. However, we

analyzed DPG during 30 minutes after bedtime to examine heat loss after bathing because some participants took a bath just before bedtime.

Another plausible mechanism for shortening SOL is sleep permitted by skin warmth. This hypothesis is supported by animal studies of the preoptic circuit, which is proposed as the mechanistic connection between body warming and ability to sleep. Skin warmth is a stimulus that enables control by molecularly defined neural circuits involving the brain hypothalamic suprachiasmatic nucleus, which controls both the neural mechanisms that include suppression of thermogenesis, vasodilation, as well as suppression of cortisol release, to initiate an earlier onset of melatonin to hasten the sleep process. Further, skin warmth could stimulate sensory inputs to preoptic nitrergic-glutamatergic neurons that initiate simultaneous nonrapid eye movement sleep and body cooling by promoting vasodilation and downregulation of brown adipose tissue thermogenesis.[35] Additionally, a human brain study using positron emission tomography showed that the hypothalamus responded to subtle changes in skin temperature.[36] In laboratory studies of humans, SOL was reported to be shortened by a subtle increase in distal skin temperature with no or limited CBT change during the time from lights-off to sleep onset.[22,23]

The clinical implications of our data could be extrapolated by comparing with the outcomes using medications and other behavioral therapies. The maximal reductions in self-reported and actigraphic SOL in the present study were 6 minutes (reduction of 20.0%) and 6 minutes (reduction of 33.3%) with bathing for 10 minutes when scheduled 2–3 hours before bedtime compared with not bathing. As for the effect of shortening SOL by medications, a review suggested that SOL was significantly decreased for benzodiazepine hypnotics (10.0 minutes; 95% CI, 3.4–16.6), nonbenzodiazepine hypnotics (12.8 minutes; 95% CI, 8.8–16.9), and antidepressants (7.0 minutes; 95% CI, 3.3–10.7).[37] Although reductions of SOL by hot-water bathing are not more than those by hypnotics, it is a safe process, with no or limited adverse effects. This is particularly beneficial to older adults, who have a high risk of excessive sedation, cognitive impairment,[10] falls that might cause traumatic brain injury or hip fracture,[11] and impaired performance of daily activities.[12] Other behavioral therapies also shorten SOL, including cognitive-behavioral therapy,[38] mindfulness meditation,[39] and exercise training.[40] However, hot-water bathing is an easier therapeutic practice for older adults because it does not require high exercise tolerance, special programs, or expensive equipment.

Despite the advantages of our current study, it does have the following limitations. First, the participants of our study were not randomly selected, which could lead to selection bias. However, some data on BMI, the proportion of antihypertensive drug use, and eGFR in our study are similar to data in a nationwide survey performed with individuals aged > 60 years.[41] Second, the generalizability of our findings to a younger population remains unconfirmed.

Third, we conducted this survey in a comparatively colder season (October to April), and monthly day-mean outdoor temperature in the study area ranges from 3.9–26.9°C across a normal year, according to the local meteorological office in Nara. An observational study conducted in Japan reported that actigraphic SOL was longer in summer than in fall or winter, although bedroom temperature in summer could cause discomfort and should have been regulated to improve sleep quality (bedroom temperature 27.7°C ± 0.63°C; relative bedroom humidity 74.0% ± 1.89%; proportion of air conditioning use 46.2%).[42] Whether outdoor temperature independently affects the association between PBH and SOL remains undetermined. Fourth, SOL is measured by wrist actigraphy. The gold standard of measuring sleep is polysomnography. Actigraphy is known to underestimate wake time compared with PSG,[43] leading to underestimation of SOL. However, actigraphy appears to be more feasible in a large-scale study of home settings than polysomnography, and we show the association of hot-water bathing with SOL by both actigraphic and self-reported evaluation. Finally, CBT modifications as an index of heat exposure or heat loss after bathing are not considered.

In conclusion, our study reveals that hot-water bathing before bedtime in home settings is significantly associated with shorter actigraphic/self-reported SOL and higher DPG in a large-scale older general population. This study in real life can enhance the generalizability of the evidence from laboratory-controlled studies and suggests optimal bathing behaviors and environments for shortening SOL.

ABBREVIATIONS

BMI, body mass index
CBT, core body temperature
CI, confidence interval
DPG, distal-proximal skin temperature gradient
eGFR, estimated glomerular filtration rate
IQR, interquartile range
PBH, passive body heating
SD, standard deviation
SOL, sleep onset latency

REFERENCES

1. Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep*. 1995;18(6):425–432.
2. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care*. 2010;33(2):414–420.
3. Troxel WM, Buysse DJ, Matthews KA, et al. Sleep symptoms predict the development of the metabolic syndrome. *Sleep*. 2010;33(12):1633–1640.
4. Schwartz SW, Cornoni-Huntley J, Cole SR, Hays JC, Blazer DG, Schocken DD. Are sleep complaints an independent risk factor for myocardial infarction? *Ann Epidemiol*. 1998;8(6):384–392.
5. Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the risk of acute myocardial infarction: a population study. *Circulation*. 2011;124(19):2073–2081.
6. Zheng B, Yu C, Lv J, et al; China Kadoorie Biobank Collaborative Group. Insomnia symptoms and risk of cardiovascular diseases among 0.5 million adults: a 10-year cohort. *Neurology*. 2019;93(23):e2110–e2120.

7. Almeida OP, Alfonso H, Yeap BB, Hankey G, Flicker L. Complaints of difficulty to fall asleep increase the risk of depression in later life: the health in men study. *J Affect Disord*. 2011;134(1-3):208–216.
8. Bubu OM, Brannick M, Mortimer J, et al. Sleep, cognitive impairment, and Alzheimer's disease: a systematic review and meta-analysis. *Sleep*. 2017;40(1): zsw032.
9. Dew MA, Hoch CC, Buysse DJ, et al. Healthy older adults' sleep predicts all-cause mortality at 4 to 19 years of follow-up. *Psychosom Med*. 2003;65(1): 63–73.
10. Lee JE, Ju YJ, Chun KH, Lee SY. The frequency of sleep medication use and the risk of subjective cognitive decline (SCD) or SCD with functional difficulties in elderly individuals without dementia. *J Gerontol A Biol Sci Med Sci*. 2020;75(9): 1693–1698.
11. Tom SE, Wickwire EM, Park Y, Albrecht JS. Nonbenzodiazepine sedative hypnotics and risk of fall-related injury. *Sleep*. 2016;39(5):1009–1014.
12. Gray SL, LaCroix AZ, Hanlon JT, et al. Benzodiazepine use and physical disability in community-dwelling older adults. *J Am Geriatr Soc*. 2006;54(2): 224–230.
13. VanSomeren EJ. More than a marker: interaction between the circadian regulation of temperature and sleep, age-related changes, and treatment possibilities. *Chronobiol Int*. 2000;17(3):313–354.
14. Kräuchi K, Cajochen C, Werth E, Wirz-Justice A. Warm feet promote the rapid onset of sleep. *Nature*. 1999;401(6748):36–37.
15. Kräuchi K, Cajochen C, Werth E, Wirz-Justice A. Functional link between distal vasodilation and sleep-onset latency? *Am J Physiol Regul Integr Comp Physiol*. 2000;278(3):R741–R748.
16. Pache M, Kräuchi K, Cajochen C, et al. Cold feet and prolonged sleep-onset latency in vasospastic syndrome. *Lancet*. 2001;358(9276):125–126.
17. Bunnell DE, Agnew JA, Horvath SM, Jopson L, Wills M. Passive body heating and sleep: influence of proximity to sleep. *Sleep*. 1988;11(2):210–219.
18. Raymann RJ, Swaab DF, Van Someren EJ. Cutaneous warming promotes sleep onset. *Am J Physiol Regul Integr Comp Physiol*. 2005;288(6): R1589–R1597.
19. Raymann RJ, Swaab DF, Van Someren EJ. Skin temperature and sleep-onset latency: changes with age and insomnia. *Physiol Behav*. 2007;90(2-3): 257–266.
20. Haghayegh S, Khoshnevis S, Smolensky MH, Diller KR, Castriotta RJ. Before-bedtime passive body heating by warm shower or bath to improve sleep: a systematic review and meta-analysis. *Sleep Med Rev*. 2019;46:124–135.
21. Seyyedrasooli A, Valizadeh L, Zamanzadeh V, Nasiri K, Kalantri H. The effect of footbath on sleep quality of the elderly: a blinded randomized clinical trial. *J Caring Sci*. 2013;2(4):305–311.
22. Chiu HY, Lin EY, Chiu HT, Chen PY. A feasibility randomized controlled crossover trial of home-based warm footbath to improve sleep in the chronic phase of traumatic brain injury. *J Neurosci Nurs*. 2017;49(6):380–385.
23. Tai Y, Saeki K, Yamagami Y, et al. Association between timing of hot water bathing before bedtime and night-/sleep-time blood pressure and dipping in the elderly: a longitudinal analysis for repeated measurements in home settings. *Chronobiol Int*. 2019;36(12):1714–1722.
24. Obayashi K, Saeki K, Iwamoto J, et al. Positive effect of daylight exposure on nocturnal urinary melatonin excretion in the elderly: a cross-sectional analysis of the HEIJO-KYO study. *J Clin Endocrinol Metab*. 2012;97(11): 4166–4173.
25. Saeki K, Obayashi K, Kurumatani N. Indoor cold exposure and nocturia: a cross-sectional analysis of the HEIJO-KYO study. *BJU Int*. 2016;117(5): 829–835.
26. Rubinstein EH, Sessler DI. Skin-surface temperature gradients correlate with fingertip blood flow in humans. *Anesthesiology*. 1990;73(3):541–545.
27. Japanese Society of Nephrology. Evidence-based practice guideline for the treatment of CKD. *Clin Exp Nephrol*. 2009;13:537–566.
28. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193–213.
29. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant*. 2013;48(3):452–458.
30. Mishima Y, Hozumi S, Shimizu T, Hishikawa Y, Mishima K. Passive body heating ameliorates sleep disturbances in patients with vascular dementia without circadian phase-shifting. *Am J Geriatr Psychiatry*. 2005;13(5): 369–376.
31. Aritake-Okada S, Kaneita Y, Uchiyama M, Mishima K, Ohida T. Non-pharmacological self-management of sleep among the Japanese general population. *J Clin Sleep Med*. 2009;5(5):464–469.
32. Campbell SS, Broughton RJ. Rapid decline in body temperature before sleep: fluffing the physiological pillow? *Chronobiol Int*. 1994;11(2):126–131.
33. Murphy PJ, Campbell SS. Nighttime drop in body temperature: a physiological trigger for sleep onset? *Sleep*. 1997;20(7):505–511.
34. Gompper B, Bromundt V, Orgül S, Flammer J, Kräuchi K. Phase relationship between skin temperature and sleep-wake rhythms in women with vascular dysregulation and controls under real-life conditions. *Chronobiol Int*. 2010;27(9-10):1778–1796.
35. Harding EC, Franks NP, Wisden W. The temperature dependence of sleep. *Front Neurosci*. 2019;13:336.
36. Egan GF, Johnson J, Farrell M, et al. Cortical, thalamic, and hypothalamic responses to cooling and warming the skin in awake humans: a positron-emission tomography study. *Proc Natl Acad Sci USA*. 2005;102(14): 5262–5267.
37. Buscemi N, Vandermeer B, Friesen C, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *J Gen Intern Med*. 2007;22(9):1335–1350.
38. Geiger-Brown JM, Rogers VE, Liu W, Ludeman EM, Downton KD, Diaz-Abad M. Cognitive behavioral therapy in persons with comorbid insomnia: a meta-analysis. *Sleep Med Rev*. 2015;23:54–67.
39. Gross CR, Kreitzer MJ, Reilly-Spong M, et al. Mindfulness-based stress reduction versus pharmacotherapy for chronic primary insomnia: a randomized controlled clinical trial. *Explore (NY)*. 2011;7(2):76–87.
40. Yang PY, Ho KH, Chen HC, Chien MY. Exercise training improves sleep quality in middle-aged and older adults with sleep problems: a systematic review. *J Physiother*. 2012;58(3):157–163.
41. Japanese Ministry of Health. Labour and Welfare. 2010 National Health and Nutrition Survey. https://www.mhlw.go.jp/bunya/kenkou/eiyou/h22-houkoku.html. Accessed June 30, 2020.
42. Okamoto-Mizuno K, Tsuzuki K. Effects of season on sleep and skin temperature in the elderly. *Int J Biometeorol*. 2010;54(4):401–409.
43. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. *Sleep*. 2003; 26(3):342–392.

ACKNOWLEDGMENTS

The authors thank Naomi Takenaka, Sachiko Sogahara, Keiko Nakajima, and Megumi Natsuaki for their valuable assistance with data collection and analysis.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September 22, 2020
Submitted in final revised form January 26, 2021
Accepted for publication January 26, 2021
Address correspondence to: Yoshiaki Tai, MD, Department of Epidemiology, Nara Medical University School of Medicine, 840 Shijocho, Kashiharashi, Nara, 634-8521, Japan; Email: yoshiaki.t@naramed-u.ac.jp

DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work for this study was performed at the authors' respective institutions. This work was supported by research funding from the Department of Indoor Environmental Medicine, Nara Medical University; JSPS KAKENHI (grant numbers: 24790774, 22790567, 25860447, 25461393, 15H04776,

15H04777, 18H06396, and 18K15899); Mitsui Sumitomo Insurance Welfare Foundation; Meiji Yasuda Life Foundation of Health and Welfare; Osaka Gas Group Welfare Foundation; Japan Diabetes Foundation; Daiwa Securities Health Foundation; Japan Science and Technology Agency; YKK AP Inc.; Ushio Inc.; Nara Prefecture Health Promotion Foundation; Nara Medical University Grant-in-Aid for Collaborative Research Projects; Tokyo Electric Power Company; EnviroLife Research Institute Co., Ltd.; Sekisui Chemical Co., Ltd.; LIXIL Corp.; and KYOCERA Corp. K.S. and K.O. received research grants from YKK AP Inc.; Ushio Inc.; Tokyo Electric Power Company; EnviroLife Research Institute Co., Ltd.; Sekisui Chemical Co., Ltd.; LIXIL Corp.; and KYOCERA Corp. The other authors report no conflicts of interest.