2024

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RUNNING TITLE: Physical Activity Temperature and Hot Flashes

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Sources of funding: National Science Foundation Grant #BCS-1848330 (Sievert and Brown) and National Institutes of Health (NHLBI) 1 R15 HL145650-01A1 (Witkowski)

Financial disclosures/conflicts of interest: None reported.

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ABSTRACT

Objective: This study determined the association between acute changes in physical activity, temperature and humidity and 24-hour subjective and objective hot flash experience.

Methods: Data collection occurred during the cooler months of the year in Western Massachusetts (October-April). Women aged 45-55 across 3 menopause stages (n=270) were instrumented with ambulatory monitors to continuously measure hot flashes, physical activity, temperature and humidity for 24-hours. Objective hot flashes were assessed via sternal skin conductance, and subjective hot flashes were recorded by pressing an event marker and data logging. Physical activity was measured with wrist-worn accelerometers and used to define sleep and wake periods. Logistic multilevel modeling was used to examine the differences in physical activity, humidity, and temperature in the 10 minutes preceding a hot flash versus control windows when no hot flashes occurred. The odds of hot flashes were considered separately for objective and subjective hot flashes as well as for wake and sleep periods.

Results: Data from 188 participants were included in the analyses. There was a significantly greater odds of a hot flash following acute increases in physical activity for objective waking hot flashes (OR=1.31, 95% CI:1.17-1.47, p<0.001) and subjective waking hot flashes (OR=1.16, 95% CI: 1.0-1.33, p=0.03). Acute increases in the actigraphy signal were associated with significantly higher odds of having an objective (OR=1.17, 95% CI:1.03- 1.35, p<0.01) or subjective (OR=1.72, 95% CI 1.52-2.01, p<0.001) sleeping hot flash. Increases in temperature were significantly related to the odds of subjective sleeping hot flashes only (OR=1.38, 95% CI:1.15-1.62, p<0.001). There was no evidence for a relationship between humidity and odds of experiencing any hot flashes.

Conclusions: These results indicate that acute increases in physical activity increase the odds of hot flashes that are objectively measured and subjectively reported during waking and sleeping periods. Temperature increases were only related to subjectively reported nighttime hot flashes.

KEY WORDS:
Physical activity; objective hot flashes; subjective hot flashes; temperature

INTRODUCTION

For about 80% of women, the years around menopause are marked by hot flashes[1,2], which are sudden heat dissipation events that generally involve cutaneous vasodilation and sweating. The etiology of hot flashes remains an active area of investigation. Freedman and Krell[3] posed a hypothesis that menopause results in a narrowed thermoneutral zone and a higher probability of exceeding the sweating threshold due to fluctuations in body temperature throughout the day. According to this hypothesis, even small changes in body temperature can cause hot flashes. This hypothesis was supported by studies in animals that showed increased sensitivity of thermoregulatory regions of the brain and heat loss with estrogen withdrawal such that skin vasodilation occurred at lower temperatures.[4,5] More recent data reveal that reduction in estradiol leads to changes in the preoptic area of the hypothalamus, known to control body temperature, causing increased activity of Kisspeptin/neurokinin B/dynorphin (KNDy) neurons.[6,7] Greater activity of KNDy neurons triggers downstream effectors, including sympathetic cholinergic activation of cutaneous vessels and sweat glands.

Physical activity has many benefits for health and wellness. Physical activity can increase body temperature and, therefore, may influence hot flash experience. Acute laboratory exercise has been used to trigger hot flashes in symptomatic women.[3] In that laboratory study, participants exercised until they experienced a hot flash or 1 hour of cycling elapsed. All women who reported a history of hot flashes experienced a hot flash in response to the exercise while asymptomatic women did not. While this laboratory trial provided important data on acute exercise and hot flashes, and evidence for the thermoneutral zone model of hot flashes, understanding whether physical activity impacts hot flash experience in ambulatory settings may be more relevant to women in their daily lives.

To date, few studies using ambulatory monitoring have addressed this question. Using subjectively reported data from behavioral diaries that were completed every 20 minutes and objective HF monitoring using sternal skin conductance, Thurston, et al.[8] found an increased likelihood of an objective hot flash after a self-reported increase in physical exertion (odds ratio [OR], 1.49; 95% confidence interval [CI], 0.99-2.25; P = 0.05). Other data from objectively assessed physical activity demonstrated that the likelihood of subjectively reported hot flashes that were not accompanied by objectively measured hot flashes was greater following an increase in physical activity in the 10 minutes prior to the hot flash (OR, 1.04; 95% CI, 1.00-1.10; P = 0.02) with no association between physical activity and objective hot flashes.[9] Elavsky et al.[10] found that performing greater amounts of moderate physical activity in a day than usual was related to more subjectively reported hot flashes; however, objective hot flashes were not assessed.

These studies highlight that physical activity during the day likely influences objectively measured and subjectively reported hot flashes. Assessment of hot flashes by subjective self-report *and* objective measures is important to capture both the perceived and unperceived experience[11]. Substantial variation in sweating patterns related to hot flashes has been reported,[12] which means that objective monitoring with electrodes and an ambulatory monitor placed on the sternum may not capture hot flashes centered on other parts of the body[12,13]. Further, women can have objectively measured hot flashes without any notable perception, and women can also report hot flashes when objective signs are not present. Both assessments are also important at night, when not all hot flashes are accompanied by awakening and awareness[14]. Therefore, concurrent objective and subjective assessment can improve our understanding of triggers and interventions to reduce hot flashes.

Temperature and humidity may also have an effect on hot flashes;[15–17] however, the data are less clear in natural settings.[18,19] Further, due to the changes in body temperature at night[15] and different aspects of temperature regulation that may be in effect during the day vs. night, the relationship between temperature and hot flashes may be different between sleep and wake periods. Measures of external temperature and humidity can help us better understand the relationships between hot flashes and physical activity as the hot flash response to physical activity may change based on ambient conditions. Therefore, the purpose of this analysis was to determine the association between acute changes in physical activity, temperature and humidity and 24-hour subjective and objective hot flashes.

METHODS

Study Design:

Data for this analysis were collected between 2019-2023 as part of a study investigating the relationship between brown adipose tissue and hot flashes. Results relating self-reported physical activity and hot flashes can be found elsewhere[20]. Potential participants were excluded if they were using hormone therapy. A total of 270 participants, aged 45-55 years underwent a single laboratory visit and were instrumented with ambulatory monitors for hot flashes, physical activity, temperature and humidity which were worn for 24 hours. Data collection occurred during the cooler months of the year in Western Massachusetts between October and April.

Participants:

Participants included premenopausal, perimenopausal, and postmenopausal individuals as categorized by the STRAW+10 criteria[21]. Premenopause was defined by regular menstruation, including lighter or heavier or more or less frequent menstruation than normal. Perimenopause was defined as menstrual cycles ≥7 days different than normal up to 12 months of amenorrhea.

Women were considered postmenopausal when amenorrhea was > 12 months. Participants were excluded if they were taking hormone therapy. The Institutional Review Boards of the University of Massachusetts Amherst and the University of Hawaii at Hilo approved the study, and all participants gave written consent.

Measures

During the laboratory visit, women participated in face-to-face interviews with semi-structured questionnaires. Data were collected on demographic information, symptom histories (23 symptoms experienced during the past two weeks), and details about their last menstrual cycles. Body mass index (BMI) was calculated from height and weight measurements (kg/m^2).

The outcomes of interest were objectively measured and subjectively reported hot flashes over 24 hours, considering waking and sleeping period hot flashes separately. Participants were equipped with a Biolog (UFI, Morro Bay, CA) ambulatory sternal skin conductance hot flash monitor with event marking buttons. The monitor recorded objective hot flashes as measured by skin conductance with two electrodes placed on either side of the sternum. Hot flashes were coded following the established criteria of an increase in 2 micromhos over 30 seconds. Some objective hot flashes did not meet the established criteria, but a substantial change in the sweating pattern was observed in concordance with the participant's subjective report. In those cases, the objective hot flash was also recorded. Participants were instructed to self-report hot flashes via pushing the button on the hot flash monitor, or, if they were unable to do so, to write the time of the hot flash on a log. Self-reported hot flashes are referred to as subjective hot flashes, and those recorded by the monitor as objective hot flashes.

Temperature and humidity were continuously recorded throughout the 24-hour period using a GSP-6 data logger (Elitech, San Jose, CA). The logger was placed in a pouch with the hot flash monitor and data probes dangled outside the pouch, exposed to the ambient conditions immediately adjacent to the participant. Participants were directed to place the monitoring pouch with temperature and humidity probes beneath the covers at night to capture their microclimate during sleeping hours.

Participants wore an Actigraph accelerometer (v6.13.4 Firmware v1.9.2, Pensacola, FL) on the wrist with an epoch length of 10 seconds for the 24-hour period. Using this actigraph data, sleep onset and wake up times were estimated by GGIR (version 2.9-0) with the sleep algorithm from Vanhees *et al.*[22]. Hot flashes were categorized as waking or sleeping based on these sleep times. Mean vector magnitude was used to measure participants' physical activity levels throughout the monitoring period. The units of the mean vector magnitude are in Actigraph counts, a measure produced by Actigraph software that summarizes acceleration within a time interval (epoch) of set length. In general, higher vector magnitude indicates higher intensity of movement.

Analysis:

For each participant, physical activity, temperature, and humidity data for the monitoring period were divided into 10-minute windows based on the times at which they had hot flashes. Any 10-minute window prior to a hot flash was considered a hot-flash window. Control windows were defined as 10-minute windows that were not within the 10 minutes. That is, for each participant, the time periods that were not within 10-minutes of a hot flash were divided into 10-minute windows, and these were defined as the control windows. The mean temperature, humidity, and vector magnitude were taken for each window, and these window-level summaries were the inputs to the analysis. Paired t-tests were conducted to compare the waking vs. sleeping period temperature and humidity

Logistic multilevel modeling (logit link) was used to examine the differences in physical activity, humidity, and temperature in the 10 minutes preceding a hot flash versus control (no hot flash) windows, while controlling for the covariates BMI and menopausal stage. These covariates were selected to control for the previously observed relationship between BMI and menopausal stage with hot flashes. Logistic regression was suitable because the outcome considered was the occurrence of a hot flash, encoded as a binary variable. The multilevel structure accounted for the fact that there were multiple windows for each participant. Separate models were fitted for objective waking hot flashes, objective sleeping hot flashes, subjective waking hot flashes, and subjective sleeping hot flashes. Our modeling approach, as described here, is similar to that of Gibson, et al.[9]

Mean vector magnitude, humidity, and temperature were person-mean-SD standardized. This choice (between person-mean centering and grand-mean centering) is based on the reasoning that we were interested in whether deviations from a participant's typical activity, temperature, or humidity were associated with having hot flashes, not deviations from the grand mean among the entire set of participants.[23]

The models presented below include random intercepts and random slopes only for physical activity. All the models were adjusted for BMI and menopausal stage as fixed effects only. Initially, due to the reasoning that the relationship between temperature or humidity and the odds of having a hot flash may also vary by participant, we also included random slopes for temperature and humidity. However, the estimates for the variance components were very small, producing a near singular fit. In order to obtain model convergence for these more complex models, we imposed noninformative priors over the covariance, fixed effects, and residuals using through the blme R package (version 1.0-5)[24]. Comparison between this more complex model and the simpler model only including a random slope for vector magnitude showed that the BIC values were lower for the simpler model relative to the more complex model, as were the AIC values, indicating that the simpler model is adequate to describe the observed data. Inspecting estimates for the random effects indicates that between-person variability was small for vector magnitude, temperature, and humidity; the 95% confidence intervals for the simpler and more complex model respectively are shown in Supplementary Table 1.

Because the addition of the random slopes for temperature and humidity had minimal impact on model fit, we proceeded with the simpler model that only included a random slope for vector magnitude. This choice did not have a major influence on inferences from the models, as the statistical significance of the variables were identical, and the effect sizes were very similar (Supplementary Table 1). The final (simpler) model was fitted with the R package lme4 (version 1.1-34)[25].

In the multilevel model, the time windows were clustered within the participants. We let i denote the index of level 1 of the data (variables at the time window level) and j denote the index of level-2 variable. The binary outcome variable Y encodes whether the i^{th} window was a 10-minute window preceding a hot flash ($Y_i = 1$) or whether it was a control window. Using the indexing notation such that $j[i]$ denotes the i^{th} observation of the j^{th} participant, the model including a random intercept by participant as well as a random slope for mean vector magnitude by participant is shown in the equation below:

$\Pr[Y_i = 1] = \text{logit}^{-1}\ \alpha_{j[i]} + \beta_{1j[i]}(\text{Activity})_i + \beta_2(\text{Temperature})_i + \beta_3(\text{Humidity})$ for window i

$\alpha_j = a_{0,0} + b_{1,0}\text{BMI}_j + b_{2,0}(\text{Perimenopausal})_j + b_{3,0}(\text{Postmenopausal})_j + \eta_{2j}$ for participant j

$\beta_{1j} = a_{0,1} + b_{1,1}\text{BMI}_j + b_{2,1}(\text{Perimenopausal})_j + b_{3,1}(\text{Postmenopausal})_j + \eta_{1j},$

where η_{1j} and η_{2j} are the level-2 error terms.

Parametric bootstrap confidence intervals for all parameters of interest were calculated with 1,000 replicates using the basic bootstrap method.

RESULTS

Out of the total of 270 participants recruited, 18 participants were excluded for missing sleep data and 3 were excluded due to missing temperature and humidity data.

For each model considering a particular hot flash outcome, a participant was included if they had at least one hot flash of the given category (e.g., a waking objective hot flash). Considering objective hot flashes, there were 143 who had at least one waking hot flash. Of these, 137 had complete temperature and humidity data and 135 also had complete BMI and menopausal stage data. With regard to sleeping objective hot flashes, there were 144 who had at least one, of which 126 had complete temperature and humidity data and 125 had complete BMI and menopausal stage data. For subjective hot flashes, there were 118 that had at least one waking hot flash. Of these, 113 had complete temperature and humidity data and 112 also had complete BMI and menopausal stage data. Lastly, there were 90 who had at least one subjective hot flash while sleeping. Of these, 78 had complete temperature and humidity data and 77 had complete BMI and menopausal stage data. In total, due to missing data, 188 participants were included in at least one of the models.

The sample included individuals across the 3 menopausal stages. Participants had a median BMI of 26.4 kg/m^2 (IQR 23.4-31.3), age of 51.2 years (IQR 49.1-53.3), and sleep duration of 8.7 hours (IQR 7.4-9.9), as shown in Table 1. The temperature and humidity were both significantly higher during sleeping hours than during waking hours, as evidenced by a P-value < 0.001 for both paired t-tests (Figure 1).

Because our outcomes were defined as 10-minute windows (hot-flash windows and control windows), the coefficients reflect the odds that a window is a hot flash window or control window. In what follows, we use the language ‘odds of having a hot flash’ to mean ‘odds of a window being a hot flash window’.

The fixed effect estimate for vector magnitude (i.e., activity intensity) was the only fixed effect that was significant across all the models (Table 2, $p < 0.05$). The odds ratio for all models exceeded 1, indicating that an increase in vector magnitude was associated with an increase in the odds of a hot flash (Table 2 and Figure 2). Because of the person-mean-SD standardization, we interpret the coefficients on the scale of the participant-level standard deviations. That is, an odds ratio of 1.31 for vector magnitude in the objective waking hot flash model indicates that a one-standard deviation increase in a participant’s vector magnitude is associated with a 1.31 times greater odds of experiencing a hot flash.

With regard to the random slope for vector magnitude, the standard deviation of the slope estimates was near zero for all models, and the 95% confidence interval contained zero for both sleeping models, indicating that the relationship between vector magnitude and the odds of the occurrence of a hot flash was not highly variable between participants. That is, increases in vector magnitude were consistently associated with increases in the odds of a hot flash across the participants. Estimates for the coefficients for mean vector magnitude by participant are shown in Supplementary Figure 1.

For temperature, our findings demonstrated a clear positive relationship between temperature and odds of experiencing a hot flash for subjective sleeping hot flashes (Table 2, OR=1.380, 95% CI 1.15-1.62) and weak evidence for this relationship for objective sleeping hot flashes (OR=1.100, 95% CI 0.993-1.22). We did not see evidence for a relationship between humidity and odds of experiencing a hot flash in any model.

Menopausal stage was not a significant predictor in most of the models. The strongest evidence for an association, however, was for subjective sleeping hot flashes, in which case the perimenopausal and postmenopausal groups had higher odds of having a hot flash relative to the premenopausal group (Table 2; OR=2.79, 95% CI 1.32-5.48 and OR=2.61,95% CI 1.24-5.04, respectively). With regard to objective waking hot flashes, neither the premenopausal nor the postmenopausal group had significantly higher odds of having a hot flash relative to the premenopausal group (Table 2), but the postmenopausal group did have significantly higher odds of having a hot flash than the perimenopausal group (Supplementary Table 2, p=0.01). For subjective waking and objective sleeping hot flashes, the association with menopausal stage was not significant.

There was little support for an association between BMI and the odds of a hot flash. The strongest evidence was for objective sleeping hot flashes, where higher BMI was associated with lower odds of a hot flash, but significant only at a significance level of p=0.10 (Table 2, OR=0.88).

DISCUSSION

In this free-living assessment of the association between physical activity in the 10 minutes directly preceding objective and subjective hot flashes and hot flash experience, we found that there was a significantly greater odds of a hot flash following acute increases in physical activity for objective waking hot flashes, and to a lesser extent, subjective waking hot flashes, and acute increases in physical activity were associated with significantly higher odds of having an objective or subjective sleeping hot flash. When evaluating the effect of temperature and humidity preceding hot flashes, we found that higher temperatures at night were associated with higher odds of subjectively experiencing a hot flash during sleeping. There was also a trend suggesting that higher temperatures at night might be associated with objective hot flashes. However, there was no relationship between temperature and hot flashes during the waking hours. This may be specific to the cooler day temperatures experienced October through April. These data support the premise that, at least during the non-summer months, physical activity and warmer ambient temperature during sleep are associated with hot flashes.

With respect to waking hot flashes, our findings using actigraphy extend the limited available literature related to acute increases in physical activity. In peri- and postmenopausal women Thurston, et al.[8] found a greater likelihood of objectively measured hot flashes following physical exertion (OR, 1.49; 95% CI, 0.99-2.25; P = 0.05) and that hot flashes were more likely after high compared with low self-reported physical effort (OR, 1.51; 95% CI, 1.18-1.95; P = 0.001). In that study, behavioral diaries were completed 3 times each waking hour. In comparison, the current analysis used actigraphy to continually measure physical activity behavior during the 24 hours. We show that increasing activity 1 standard deviation above an individual's mean activity increases the odds of an objective hot flash by 31%, assuming other covariates are held constant. Together, these studies suggest that increases in physical activity can precede objective hot flashes.

Waking subjective experiences of hot flashes are also important to understand with respect to physical activity, as they reflect perception. We aimed to understand the subjective experience independent of whether it aligned with objective measures and found that increases in physical activity were associated with a significant, albeit smaller likelihood of subjective hot flashes. Gibson, *et al.*[9] employed a Biolog accelerometer to assess physical activity with a similar 10-

minute window analytic approach as the current study but categorized hot flashes as objective, subjective, concordant, and subjective not concordant with objective. They found that only the subjectively reported hot flashes not corroborated by objective type were preceded by increases in physical activity in the 10 minutes prior to the hot flash (OR: 1.04, 95% CI:1.00-1.10, p=0.02). Other data supporting an association between increased physical activity and daytime subjective hot flashes comes from Elavsky, et al.[10] who used hip-worn accelerometry and performed a within-person analysis to show that when people had more moderate physical activity than usual, they reported more subjective hot flashes. A key difference between the current study and these studies is the placement and type of accelerometer (e.g., hip vs. wrist). Accelerometers placed at the hip are better at measuring moderate to vigorous exercise[26] whereas wrist placement may be better at detecting activities of daily living with more upper extremity movement and movement during sleep.[27]

Our analysis showed acute increases in activity prior to both subjectively reported and objectively measured hot flashes during the sleep period. In fact, the largest effect size out of all of the models was for subjective sleeping hot flashes. Wrist actigraphy is a valid way to assess sleep in home environments[28] and has recently been employed to assess sleep characteristics and disruption due to vasomotor symptoms.[14] These data and studies using polysomnography[29,30] show that disruptions frequently occur around objectively measured hot flashes. Indeed, Freedman[15,31] showed that arousals and awakenings occur in the minutes before and after objective hot flashes at night and may depend on the stage of sleep. In our analysis, greater odds of objective and subjective hot flashes were associated with increased activity in the minutes prior to the hot flash. These findings support the premise that disturbances in sleep can occur prior to an objective or subjective hot flash.

We observed a higher odds of subjective hot flashes at night following acute increases in activity compared with objective hot flashes (OR, 1.72 vs. 1.17, respectively). This observation may be due to the fact that subjective hot flash reporting is more dependent upon awareness and, therefore, it is more likely the participant was awake and more active compared with other times during the sleep period. During the sleep period there was also a difference in odds of subjectively reported (OR, 1.38; CI, 1.15-1.62) vs. objectively measured (OR, 1.1, CI, 0.99-1.22) hot flashes at night following acute increases in temperature. At night it may be difficult for an individual to distinguish between the experience of a hot flash from a night sweat. Hot flashes are defined objectively as distinct rapid increases in skin conductance whereas night sweating has a more gradual onset and tends to be more prolonged.[18,32] At night an individual may be less aware of the nature of the experience and attribute perceptions of warmth that may be non-hot flash sweating to hot flashes. The acute increases in activity and temperature prior to subjective hot flashes may also be related, as increases in core body temperature can lead to awakenings and subsequent reporting of perceived hot flashes. However, further studies are needed to confirm this hypothesis.

We observed a significant difference in temperature during wake and sleep periods that corresponded to differences in the potential effect of temperature during waking and sleeping hours. In particular, we observed a lack of evidence for an effect of temperature during waking hours, with a significant positive association between temperature and odds of a hot flash during sleeping hours for subjective sleeping hot flashes and, with less confidence, for objective sleeping hot flashes (Table 2 and Figure 2). In the current study, participants were instructed to place the monitors under the covers with them at night and during the day monitors were worn in a pouch outside their clothes with probes exposed to the ambient air. Therefore, the temperature data at night reflect the microclimate under the covers and during the day the temperature data reflect exposure to the surrounding air. Since the study occurred during the non-summer months, mean waking temperatures were lower than mean sleeping temperatures. The temperature under the covers could have also been amplified by hot flashes and night sweating or influenced by other external conditions, such as sleeping with a partner.

The relation between temperature and hot flash experience is equivocal. Kronenberg and Barnard showed that spending 8 hours in a temperature-controlled chamber with a higher temperature (31℃) was associated with a higher hot flash frequency than in a cooler environment (19℃)[16]. In a laboratory study where participants underwent mild heating via a water-perfused suit, only approximately 40% of women had an objective hot flash.[33] In a survey of self-reported hot flashes across 54 populations, subjective hot flashes were negatively associated with winter temperatures, and women living in seasonal climates reported more hot flashes[19]. In Bangladesh and London, women wore hot flash monitors from 11:00 to 19:00, and mean ambient temperatures and humidity levels were obtained from the Central Climate Unit of the Met Office, UK, at 12:00 and 18:00. The self-reported frequency of hot flashes (e.g., 1/day) was positively correlated with ambient temperatures at 12:00 ($r=0.38$, $p<0.05$), and tended to be correlated with temperature at 18:00 ($r=0.32$, $p=0.08$). There was no correlation between self-reported hot flashes and humidity, and objectively measured hot flashes were not associated with temperature or humidity[18]. In Spain and three South American countries, higher temperatures and humidities were associated with more frequent and problematic hot flashes[17].

This study has several strengths, including the ambulatory 24-hour objective and subjective assessment of hot flashes with separate analyses during wake and sleep periods, objective actigraphic measures of physical activity, and a large sample size that includes women across menopausal stages. A limitation is the use of raw vector magnitude as this activity measure does not allow for a clear interpretation of physical activity intensity. An alternative would be to use cutpoints of activity counts to interpret activity intensity; however, currently, there is much debate about the accuracy and validity of various cutpoints for wrist worn actigraphy, and the choice of any cutpoint may vary interpretation as observed in the analysis by Elavsky, et al.[10] As algorithms develop for wrist worn actigraphy, studies will be able to apply them to research related to physical activity and hot flashes. Another limitation is the lack of measurement of core body temperature. Core temperature may or may not change prior to a hot flash.[3,33] Therefore, similar to physical activity, an increase can lead to a hot flash, but it is not obligatory. Finally, our sample is mostly of European descent and well-educated. Future research should include people from a greater diversity of backgrounds.

CONCLUSIONS

These data indicate that there are significantly higher odds of acute increases in physical activity preceding both objective and subjective hot flashes during waking and sleeping periods. The results support differences in the association between increases in temperature and hot flash experience in waking vs. sleeping periods with stronger associations with subjectively reported compared with objectively measured hot flashes at night.

These results can be used to inform patients that acute increases in physical activity during the day may be followed by hot flashes; however, physical activity has numerous benefits to health, and women should not be discouraged from physical movement at midlife. Further, restlessness and increased microclimate temperature at night may precede hot flashes, therefore environmental and behavioral measures (e.g., lighter blankets and fans) may provide benefit.

ACKNOWLEDGEMENTS: We thank Tory Vazquez, Rachel Goldstein, Akanksha Nagarkar, Liana Muñoz, Ambrine Bellou, Ashley Boudreau, Alessandra Loffredo, Mia Lipman-Tessicini, and Ava Warner for their assistance with data collection. We especially thank Amanda Paluch and all of the women who participated in this study.

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Figure Legends:

Figure 1: Mean temperature and humidity during waking and sleeping hours. Each point represents the mean for a particular participant across waking or sleeping hours. Results of a paired t-test are shown for both temperature and humidity. Both demonstrate that temperature and humidity are significantly higher during sleeping hours compared to waking hours.

Figure 2: 95% confidence intervals for odds ratio estimates of the fixed effects, across the models considering objective waking hot flashes, subjective waking hot flashes, objective sleeping hot flashes, and subjective sleeping hot flashes. Only continuous variables (which includes all variables except menopausal stage) are shown here for ease of interpretation on the same scale. All continuous variables were person-mean-SD standardized. Physical activity (vector magnitude) was also included as a random effect.

Supplemental Digital Content: Final Multilevel Supplement updated.pdf

Table 1: Participant Characteristics

Characteristic	**N = 188**
Menopausal Stage, n (%)	
Premenopausal	32 (17.0%)
Perimenopausal	78 (41.5%)
Postmenopausal	78 (41.5%)
BMI (kg/m²)	26.4 (23.4-31.3)
Age	51.2 (49.1-53.3)
Education, n (%)	
High School or Less	12 (6.4%)
Some College or College Graduate	78 (41.5%)
Higher than College Education	98 (52.1%)
Sleep Duration (hours)	8.7 (7.4-9.9)
Temperature (ºC)	
Waking Temperature	22.5 (21.3-24.1)
Sleeping Temperature	28.0 (23.4-31.7)
Humidity (%)	
Waking Humidity	37.4 (32.1-44.2)
Sleeping Humidity	43.4 (38.5-49.9)

Characteristics represent participants included in at least one of the models. Waking temperature and humidity were calculated as the mean across waking hours, and sleeping temperature and humidity were calculated as the mean across actigraphy-defined sleeping hours. Data are median (Interquartile Range) unless otherwise noted. BMI, Body Mass Index.

Table 2: Odds Ratios for the Fixed Effects for All Models

Variable	Estimate	95% Bootstrap CI	P-value
Objective Waking Hot Flashes			
BMI	1.14	(0.94-1.38)	0.19
Humidity	1.01	(0.92-1.12)	0.86
Perimenopausal	1.02	(0.53-1.99)	0.95
Postmenopausal	1.70	(0.90-3.25)	0.12
Temperature	1.02	(0.92-1.13)	0.73
Physical Activity	1.31	(1.17-1.47)	≤ 0.001[a]
Subjective Waking Hot Flashes			
BMI	1.06	(0.90-1.27)	0.49
Humidity	1.03	(0.93-1.14)	0.62
Perimenopausal	1.42	(0.72-2.72)	0.28
Postmenopausal	1.93	(1.06-3.5)	0.04[c]
Temperature	1.04	(0.91-1.15)	0.56
Physical Activity	1.16	(1-1.33)	0.03[c]
Objective Sleeping Hot Flashes			
BMI	0.88	(0.77-1.02)	0.09[d]
Humidity	1.03	(0.93-1.14)	0.59
Perimenopausal	0.98	(0.65-1.51)	0.93
Postmenopausal	1.08	(0.71-1.64)	0.72
Temperature	1.10	(0.99-1.22)	0.08[d]

Table 2: Odds Ratios for the Fixed Effects for All Models

Variable	Estimate	95% Bootstrap CI	P-value
Physical Activity	1.17	(1.03-1.35)	≤ 0.01[b]
Subjective Sleeping Hot Flashes			
BMI	0.92	(0.74-1.13)	0.42
Humidity	0.99	(0.85-1.18)	0.92
Perimenopausal	2.79	(1.32-5.48)	≤ 0.01[b]
Postmenopausal	2.61	(1.24-5.04)	≤ 0.01[b]
Temperature	1.38	(1.15-1.62)	≤ 0.001[a]
Physical Activity	1.72	(1.52-2.01)	≤ 0.001[a]

Odds ratio estimates for the fixed effects of each model. Confidence intervals are parametric bootstrap intervals calculated with the basic interval method using 1,000 replicates. [a]P-value ≤ 0.001, [b]P-value ≤ 0.01, [c]P-value ≤ 0.05, [d]P-value ≤ 0.10. Reported P-values are from Wald Z-tests. Physical activity is equivalent to the mean vector magnitude. BMI, Body Mass Index.

Figure 1 Revised

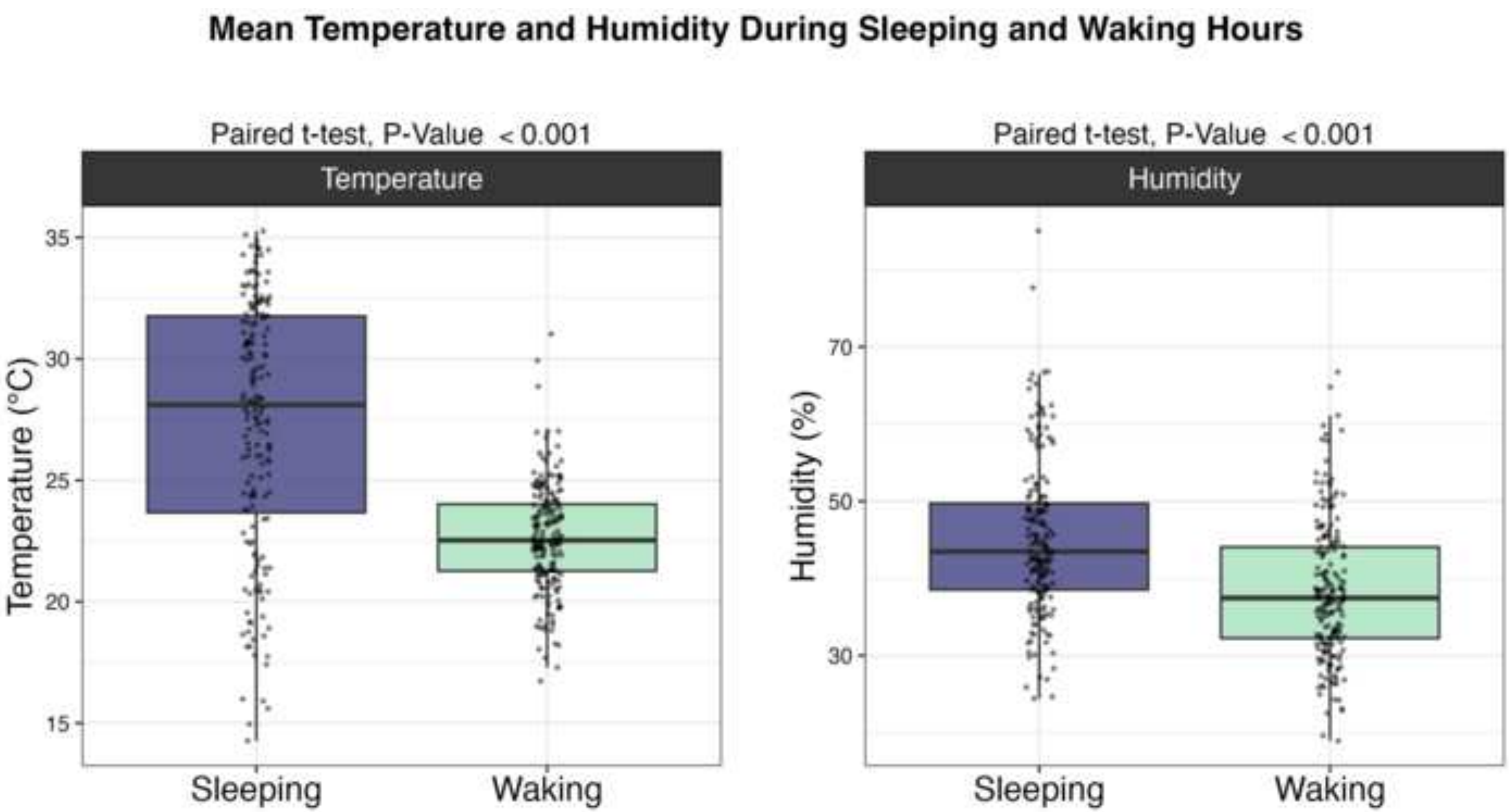
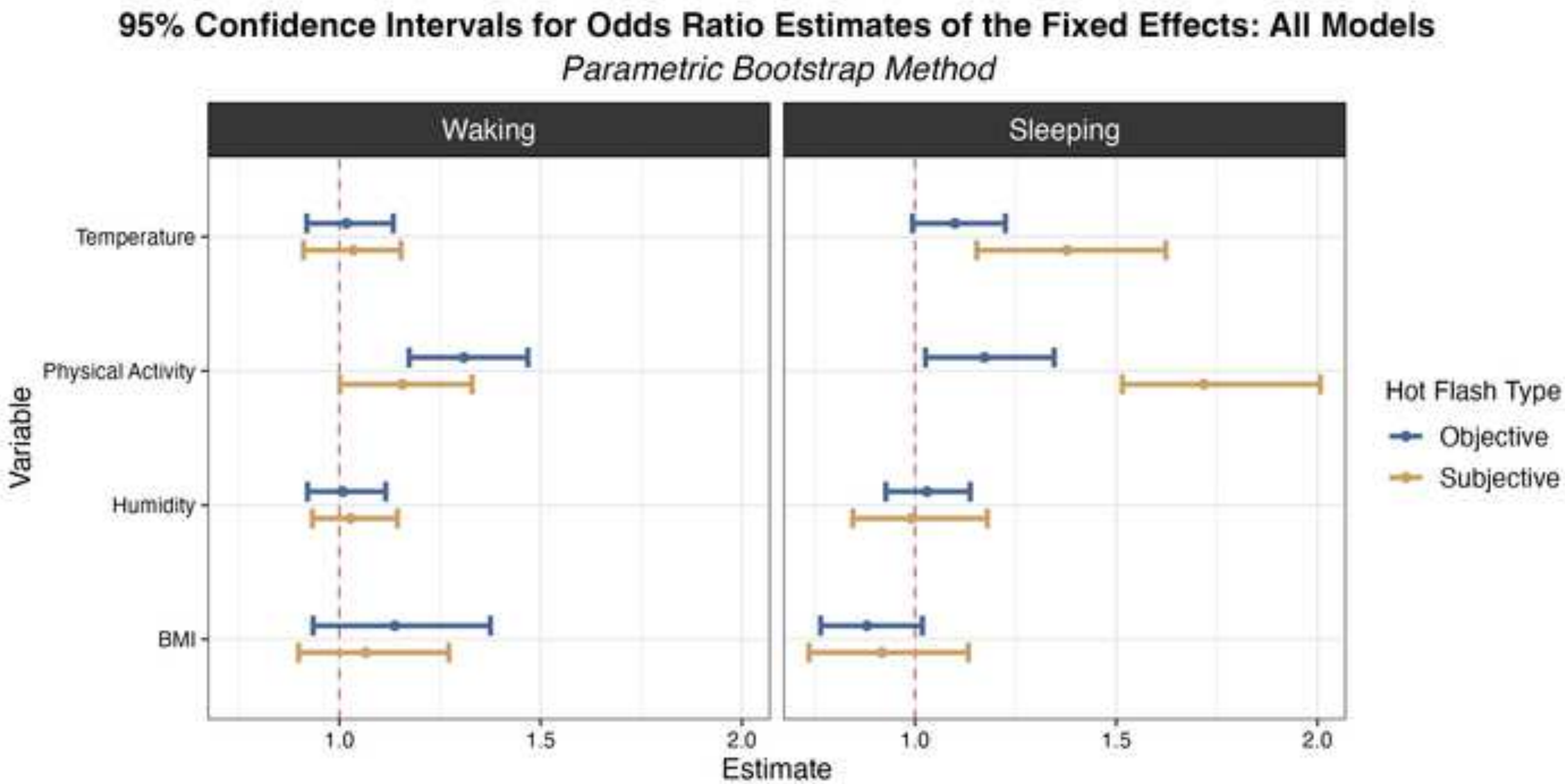


Figure 2 Revised



TITLE: Acute Increases in Physical Activity and Temperature Influences Hot Flash experience in Midlife Women

Two Sentence Summary

This study used logistic multilevel modeling to measure the association between acute changes in physical activity, temperature and humidity and 24-hour subjective and objective hot flash experience. Objective and subjective hot flashes were more likely after acute increases in physical activity whereas increases in temperature were only related to subjectively reported nighttime hot flashes with no effect of humidity.