

Is core temperature the trigger of a menopausal hot flush?

Helen Jones, PhD,¹ Tom G. Bailey, PhD,² David A. Barr, PhD,¹ Madeleine France, MPhil,¹
Rebekah A. I. Lucas, PhD,³ Craig G. Crandall, PhD,⁴ and David A. Low, PhD¹

Abstract

Objective: Menopausal hot flushes negatively impact quality of life and may be a biomarker of cardiovascular and metabolic disease risk; therefore understanding the physiology of hot flushes is important. Current thinking is that a small elevation (~ 0.03 - 0.05°C) in core temperature surpasses a sweating threshold (that is reduced in the menopause), sweating is activated, and a hot flush ensues. Nevertheless, more recent studies examining thermoregulatory control question whether core temperature per se can explain the trigger for a hot flush. The primary aim of this study was to assess the contribution of increases in core temperature on the occurrence of menopausal hot flushes.

Methods: For this purpose, 108 hot flushes were objectively assessed in a laboratory setting in 72 symptomatic postmenopausal women (aged 45.8 ± 5.1 years; body mass index $25.9 \pm 4.5 \text{ kg/m}^2$) from five previously reported studies. Women rested, wearing a tube-lined suit (or trousers), which was perfused with 34°C water. A subset then underwent mild heat stress (48°C water). Sweat rate, skin blood flow, blood pressure, heart rate, skin, and core temperature were measured continuously throughout. A hot flush was objectively identified during rest (spontaneous hot flush) or mild heating as an abrupt increase in sternal sweat rate. Further, a subset of symptomatic postmenopausal women ($n = 22$) underwent whole-body passive heating for 60 minutes to identify core temperature thresholds and sensitivities for sweat rate and cutaneous vasodilation, which were compared to a subset of premenopausal women ($n = 18$). Data were analyzed using *t* tests and/or general linear modeling, and are presented as mean (95% confidence interval).

Results: In the 20 minutes before a spontaneous hot flush, core temperature increased by $0.03 \pm 0.12^{\circ}\text{C}$ ($P < 0.05$), but only 51% of hot flushes were preceded by an increase in core temperature. During mild heating, 76% of hot flushes were preceded by an increase in core temperature. The temperature thresholds for sweating were similar, but the vasodilatory threshold was higher in postmenopausal compared with premenopausal women (37.1 ± 0.2 vs $36.8 \pm 0.3^{\circ}\text{C}$; $P = 0.06$).

Conclusion: We provide new evidence that menopausal hot flushes are unlikely triggered by an increase in core temperature. These findings provide important information about the physiology of hot flushes that have implications for treatment and management options for menopausal hot flushes.

Key Words: Core temperature – Hot flush – Menopause – Thermoregulation.

The vast majority of women experience hot flushes during the menopause,¹ which cause significant reductions in quality of life^{2,3} and increase the risk of metabolic and cardiovascular disease.^{4,5} Therefore, understanding the physiology of hot flushes in symptomatic women is important. Hot flushes are characterized by subjective

feelings of intense heat, and also peripheral vasodilation,⁶ and are physiologically defined as increases in chest sweating ($>0.002 \text{ mg/cm}^2/\text{min/s}$) or sternal skin conductance ($>2 \mu\text{mho}/30 \text{ s}$). Nevertheless, the trigger for the onset of a hot flush is not fully established. Alterations in the thermoregulatory⁷ and sympathetic nervous systems⁸ have been implicated as triggers for a hot flush, as have changes in neurotransmitters in the brain.^{9,10}

Freedman (1995) proposed that hot flushes are triggered by small increases in core temperature, ranging from 0.03 to 0.05°C . This conclusion was based on both laboratory and ambulatory studies^{11,12} of continuously measured core temperature and sternal skin conductance in postmenopausal females. For example, in one study, 65% of hot flushes in 8 women during sleep were preceded by an increase in core temperature of $\sim 0.035^{\circ}\text{C}$ within a 30-minute window preceding the hot flush event.¹³ In a subsequent study, they reported that symptomatic postmenopausal women (ie, those who experience frequent hot flushes) display a reduced core

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From the ¹Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, England; ²Centre for Research on Exercise, Physical Activity and Health, School of Human Movement and Nutrition Sciences, The University of Queensland, Australia; ³School of Sport, Exercise and Rehabilitative Sciences, University of Birmingham, Birmingham, UK; and ⁴Department of Internal Medicine, University of Texas Southwestern and Texas Health Presbyterian Hospital Dallas, TX. Funding/support: Part of this project was supported by the NIH, National Institute on Aging (AG030189).

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Address correspondence to: Helen Jones, PhD, Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Tom Reilly Building, Byrom Street, Liverpool L3 3AF, UK.
E-mail: h.jones1@ljmu.ac.uk

temperature range between the onset of shivering and sweating, when compared with asymptomatic women (ie, no flushes).¹⁴ This narrower core temperature range was primarily characterized by a lower core temperature threshold for the onset of sweating, but it is currently unknown if such temperature thresholds change during the menopause, for example, relative to premenopausal women. Taken together, these findings suggested that when an increase in core temperature surpasses the lowered sweating threshold, sweating is activated and a hot flush will ensue.

The notion that a hot flush is triggered by an increase in core temperature exceeding the sweating threshold persists, despite later findings from the same group that reported natural fluctuations in core temperature across a 24-hour period that are similar in symptomatic and asymptomatic women¹⁵; symptomatic women can and frequently do have increases in core temperature of similar magnitude (ie, 0.035°C) that do not trigger a thermoregulatory response and/or a hot flush¹⁵; and no change in hypothalamic activity (as a marker of change in core temperature), via functional magnetic resonance imaging, before and during a hot flush.¹⁶ When taken together, it is possible that increases in core temperature per se do not accurately explain the trigger for a hot flush. This information is important given that the current understanding regarding increases in core temperature triggering hot flushes has contributed to recommendations for postmenopausal women to avoid situations of environmental heat stress, including to dress appropriately, and to avoid exercise, as advocated in recent guidelines (The North American Menopause Society).¹⁷ Therefore, the primary aim of this study was to assess the contribution of increases in core temperature to the occurrence of menopausal hot flushes. A secondary aim was to compare the sweating and vasodilatory temperature thresholds between symptomatic postmenopausal and premenopausal women.

METHODS

Participants

In 72 postmenopausal women (aged 45.8 ± 5.1 years; body mass index 25.9 ± 4.5 kg/m²), we performed a secondary analysis of 108 hot flushes from five experimental studies that were designed for unrelated purposes.^{8,18-21} Studies were performed in laboratories in TX, USA or Liverpool, UK, either in the morning after an overnight fast or early afternoon at least 2 hours postprandial. Participants refrained from alcohol and exercise for 24 hours, and caffeine for 12 hours before data collection. Participants were amenorrheic for at least 12 months and were experiencing at least four hot flushes a day, as verified by a 7-day hot flush frequency questionnaire.²² Participants were free from cardiovascular and metabolic diseases, and were not taking hormone therapy or any other treatments to alleviate hot flush symptoms. To compare sweating and vasodilatory threshold responses in menopausal women with that observed in nonmenopausal individuals, additional data were obtained from 18 premenopausal women.²³ Measurements in all studies were collected using

the same experimental procedures. Participants were provided with both written and verbal explanations of all study procedures, and gave written consent before enrolling in the study. All procedures and written consents were approved by the Research Ethics Committee/Institutional Review Board at each Institution.

Experimental protocol

Measurements were conducted in a temperature-controlled laboratory (24-26°C). Participants were placed in a tube-lined jacket and trousers (Med-Eng., Ottawa, Canada), which covered the entire body except for the head, feet, and the forearm (n = 52),^{8,18,20} or just wore the trousers with a loose fitting t-shirt (n = 20).^{19,21} Participants rested in a semirecumbent position for 30 minutes, while water (34°C) was perfused through the garments to control skin temperature. A subset of participants (n = 23) were then exposed to mild warming by perfusing water at 40 to 44°C through trousers to increase skin temperature in an attempt to provoke hot flashes.^{19,21} Similarly, a subset of postmenopausal (n = 22) and premenopausal (n = 18) women were exposed to whole-body passive heating by perfusing 48°C water through both the top and bottom garments for ≥ 60 minutes. Participants were monitored throughout passive heating for 60 minutes or until a 1°C increase in core body temperature occurred.

Measurements

Heart rate (HR) was obtained from an electrocardiogram (PowerLab, AD Instruments, Oxford, UK; or Space-Labs, Redmond, WA), alongside with continuous beat-by-beat finger arterial blood pressure (BP) (Finapres, Amsterdam, Netherlands). To verify continuous BP measured at the finger, an automated blood pressure (Dinamap, Gersweiler, Germany or SunTech Medical Instruments, Raleigh, NC) was obtained at regular intervals. Mean skin temperature was measured via the average of thermocouples (error 0.18°C²⁴) at the chest, upper back, lower back, abdomen, thigh, and calf,^{8,19,20} or chest, tricep, calf, and thigh,¹⁸ attached to the skin. Core temperature was measured from an ingestible pill telemetry system taken at least 2 hours before the commencement of data collection (CoreTemp, HQ_{Inc}, Palmetto, FL; error 0.02°C²⁵). Local sweat rate was recorded continuously from the dorsal forearm and the mid-sternum (not covered by the water-perfused suit) using capacitance hygrometry. Dry 100% nitrogen gas was supplied through acrylic capsules (surface area 2.32 or 2.83 cm²) attached to the skin's surface at a flow rate of 150 mL/min, with the humidity of the gas flowing out of the capsules measured by a capacitance hygrometer (Viasala, Helsinki, Finland; error 0.44 RH%²⁶). Local cutaneous blood flow was also measured at the forearm and chest using laser-Doppler flowmetry probes (Periflux System 5001, Perimed AB, Jarfalla, Sweden or Moor Instruments, Wilmington, DE). Laser Doppler flow probes were affixed with an adhesive heating ring in close proximity to each ventilated sweat rate capsule or the sweat rate capsule was attached to the Laser Doppler probe. Data were sampled

TABLE 1. The magnitude (mean ±SD) and direction (%) of change in core temperature in the 20 minutes preceding (minute immediately before minus time point 19) spontaneous hot flushes (n = 52), and those that occurred during mild heating (n = 56)

	Spontaneous hot flushes				Hot flushes during mild heating			
	T _c , °C	↑	↔	↓	T _c , °C	↑	↔	↓
Uncorrected	0.03 ± 0.12	24 (51%)	4 (4%)	21 (45%)	0.13 ± 0.17	41 (76%)	0 (0%)	13 (24%)
Corrected	-0.04 ± 0.12	16 (36%)	1 (2%)	27 (61%)	0.15 ± 0.20	36 (72%)	0 (0%)	14 (28%)

Gut temperature delay correction 5 minutes in normothermia (spontaneous) and 10 minutes in hyperthermia (mild heating). T_c, core temperature.

at 50 Hz (PowerLab, AD Instruments, Oxford, UK; or Biopac Systems, Santa Barbara, CA; error 2 AU²⁷). Cutaneous blood flow was divided by mean arterial pressure to provide cutaneous vascular conductance (CVC).

Hot flush identification

The onset of a hot flush was objectively identified as a transient and pronounced spontaneous increase in sternal sweat rate (>0.002 mg/cm/min/s), during both normothermia (n = 52) and passive heating (n = 56). Participants also informed the researcher of a self-reported feeling of a hot flush and again once the feeling had dissipated. The end of each hot flush was objectively identified as the return of sweat rate to pre hot flush baseline values, inclusive of any hot flushes during passive heating. Because of the variance in the

length of hot flushes, each hot flush episode was divided into eight equal segments, with each segment representing 12.5% of hot flush duration. Sweat rate data were evaluated at the following time points: pre-flush baseline (2 minutes), the final 5-second period at the end of each of the aforementioned segments, and for 2 minutes after the end of the hot flush. After the identification of a hot flush, data were extracted from the 20-minute period before the flush, and also after the flush, in 1-minute averages.

Identification of core temperature change before a hot flush

To identify the core temperature responses before each hot flush, we first identified the 20-minute period before the onset of the hot flush. The frequency of at least a 0.01°C increase,

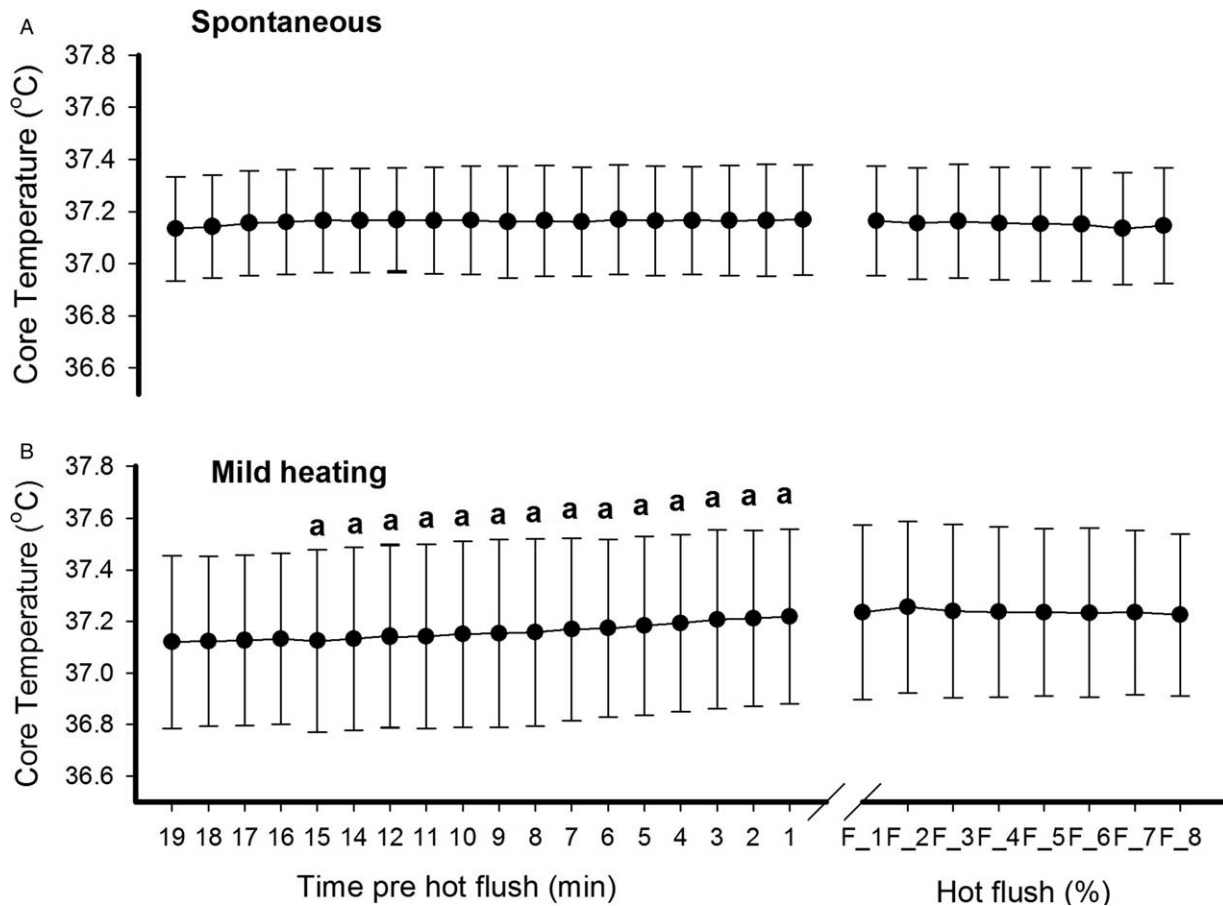


FIG. 1. The magnitude of change in core temperature in 20 minutes before and during a (A) spontaneous hot flush (n = 52); and (B) during mild heating (n = 56) (mean ± SD). ^aIndicates a difference relative to time point 19 before the hot flush.

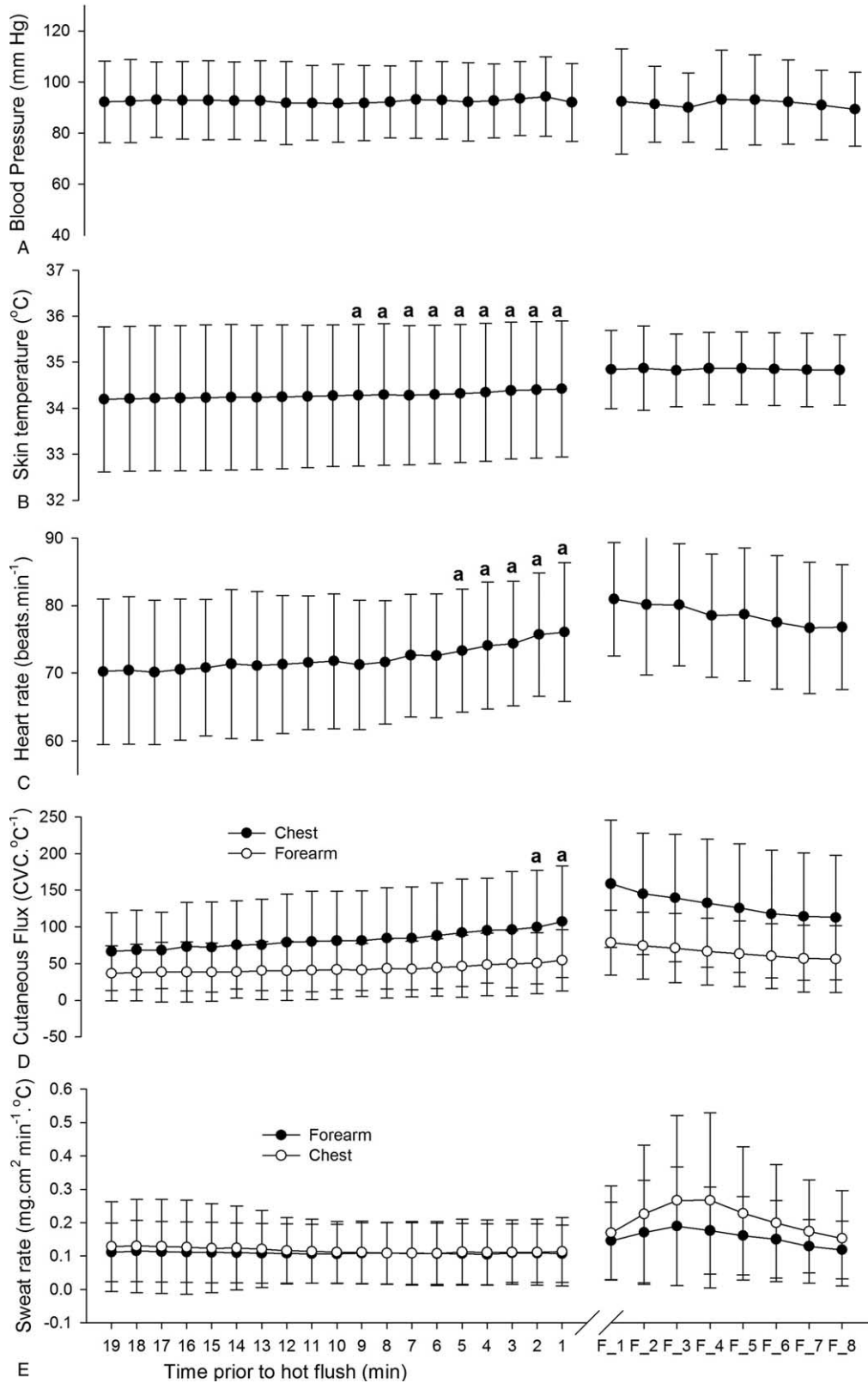


FIG. 2. The magnitude of change in (A) blood pressure, (B) heart rate, (C) skin temperature, (D) chest and forearm skin blood flow, and (E) chest and forearm sweating in the 20 minutes before and during a spontaneous hot flush (mean ± SD). ^aIndicates an increase relative to time point 19 before the hot flush.

decrease, or no change in core temperature are presented as a count (and as a percentage) in Table 1, along with the overall mean change in core temperature that occurred in the 20 minutes before the objective onset of all hot flushes. In an attempt to accommodate for a potential time lag in gut temperature compared with the gold standard pulmonary artery temperature,²⁸ we also arbitrarily shifted the gut temperature values back by 5 minutes in normothermia and 10 minutes²⁸ during passive heating (Table 1).

Identification of temperature thresholds and sensitivities for sweating and cutaneous vasodilation in response to passive heating

The goal of whole-body heat stress is an increase in core temperature to enable examination of temperature thresholds (temperature at which cutaneous vasodilation and/or sweating begins) and sensitivities (the rise in skin blood flow or sweat produced after the temperature threshold) for sweating and cutaneous vasodilation. For this purpose, the temperature thresholds for the onset of sweating (mean body temperature) and cutaneous vasodilation (core body temperature) were calculated in a blinded fashion by the same analyst for each study,²⁹ and are reported as the change from normothermic baseline. The sensitivity of the sweating responses were estimated from the slope of the relationships between sweat rate and mean body temperature beyond the mean body temperature threshold for the onset of sweating and any sweat

rate plateau. Skin blood flow sensitivity was estimated in the same way, but using the rate of CVC per unit change in core temperature. This was calculated for $n = 22$ postmenopausal and $n = 18$ premenopausal women who underwent whole-body passive heating for 60 minutes.^{23,30}

Statistical analysis

To examine whether core temperature (and other thermoregulatory variables) increased before a hot flush, one-way repeated-measures general linear models were employed with a factor of time (19 levels). Significant main effects of time were followed up with least significant difference uncorrected planned comparisons comparing each time point before the onset of the hot flush relative to time point 19 (ie, 19 minutes before onset of hot flush). Independent-sample *t* tests were employed for the comparison of temperature thresholds for sweating and cutaneous vasodilation between premenopausal and postmenopausal women. Data are presented as mean and 95% confidence intervals (CIs) unless otherwise stated.

RESULTS

Identification of core temperature change preceding a spontaneous hot flush

We observed 52 hot flushes (ie, spontaneous hot flushes) in 34 women. The mean change in core temperature across the 20-minute period before a hot flush was $0.03 \pm 0.12^\circ\text{C}$ (Table 1). The main effect of time was statistically significant

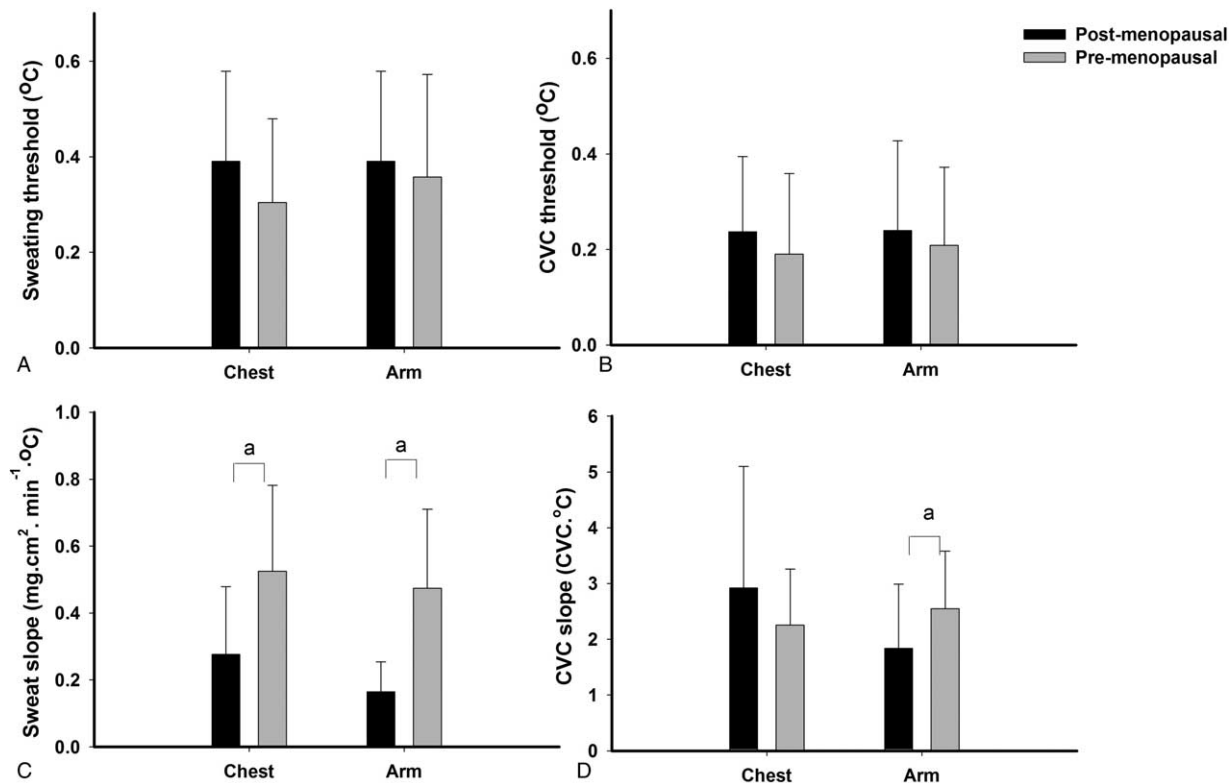


FIG. 3. Comparison of post ($n = 22$) and premenopausal ($n = 18$) women during a whole-body heat stress. (A) The change in mean body temperature threshold from normothermic baseline to the onset of chest and forearm sweating; (B) sweat rate sensitivity (slope) at the chest and forearm; (C) the change in core temperature threshold from normothermic baseline to the onset of chest and forearm cutaneous vasodilation; (D) skin blood flow sensitivity (slope) at the chest and forearm (mean \pm SD). ^aIndicates significant difference between post and premenopausal women ($P < 0.05$).

over the 20-minute period ($P < 0.01$), but there was no significant increase at any time point before the hot flush relative to time point 19. When counted, only 51% of hot flushes were actually preceded by a core temperature increase of at least 0.01°C across the prior 20 minutes time period; thus 49% of the hot flushes were not preceded by an increase in core temperature. When the correction for a potential time lag in gut temperature (ie, 5 minutes delay) was applied, mean core temperature did not show an increase ($-0.04 \pm 0.12^{\circ}\text{C}$) and only 36% of the hot flushes were preceded by a core temperature increase (Table 1). Nevertheless, there was still a statistically significant change in core temperature over the 20 minutes preceding the hot flush, but this was a core temperature decrease rather than an increase ($P < 0.05$).

Identification of core temperature change preceding a hot flush during mild heating

We observed a total of 56 hot flushes from 39 women during mild heating. The mean change in core temperature across the 20-minute period before a hot flush was $0.13 \pm 0.20^{\circ}\text{C}$ (Table 1). The main effect of time was statistically significant over the 20-minute period ($P < 0.01$). As illustrated in Fig. 1, relative to time point 19, core temperature was statistically higher 12 minutes before the hot flush and remained higher thereafter until the flush onset. Only 76% of hot flushes were preceded by a core temperature increase. When the correction for the time lag in gut temperature during heating (ie, 10 minutes delay) was applied, core temperature increased by $0.15 \pm 0.17^{\circ}\text{C}$ ($P < 0.05$), and 72% of the hot flushes were preceded by a core temperature increase (Table 1).

Physiological responses that precede a spontaneous normothermic hot flush

In the 20-minute period preceding a hot flush event, there were increases in mean skin temperature, HR, and also chest and forearm skin blood flow (main effects of time, $P < 0.05$). As illustrated in Fig. 2, the following are the times before the hot flush when the indicated variables were significantly elevated relative to time point 19: heart rate 3 minutes before, chest and forearm skin blood flow 1 minute before, whereas mean skin temperature was elevated at all time points relative to time point 19. Sweating and arterial blood pressure did not change during the 20-minute period before a hot flush (main effect of time; $P > 0.05$; Fig. 2).

Temperature thresholds and sensitivities for sweating and cutaneous vasodilation in response to 60 minutes of whole-body passive heating: the change in mean body temperature from normothermic baseline to the onset of chest and forearm sweating was similar between post and premenopausal women ($P > 0.14$; Fig. 3). After the onset of sweating during the whole-body heat stress, the rate of chest and forearm sweating was 0.25 ($0.10, 0.40$) $\text{mg}/\text{cm}^2/\text{min}/^{\circ}\text{C}$ and 0.31 ($0.18, 0.43$) $\text{mg}/\text{cm}^2/\text{min}/^{\circ}\text{C}$ lower, respectively, in post compared to premenopausal women ($P < 0.001$; Fig. 3).

The change in core temperature from normothermic baseline to onset of chest and forearm cutaneous vasodilation

was similar in post compared with premenopausal women ($P > 0.37$; Fig. 3). The rate of cutaneous vasodilation at the chest was similar in post compared with premenopausal women ($P = 0.21$), whereas this value was lower in post compared with premenopausal women ($P = 0.04$; Fig. 3).

DISCUSSION

The aim of this study was to assess the contribution of increases in core temperature on the occurrence of menopausal hot flushes. We provide new evidence that small/subtle changes in core temperature in symptomatic postmenopausal women are unlikely to be the trigger for a hot flush, given that not all flushes were preceded by an increase in core temperature, even during mild heating, coupled with similar sweating thresholds between symptomatic postmenopausal and young premenopausal women. Collectively, these data provide important insight into the physiology of hot flushes and have implications for treatment and management for hot flushes.

We examined the core temperature responses before hot flushes that occurred in normothermic women (referred to as spontaneous hot flushes). We observed 52 hot flushes from 34 women, with only 51% of hot flushes preceded by any increase in core temperature, which, on average, was an increase of $\sim 0.03^{\circ}\text{C}$. Put another way, 49% of the hot flushes were not preceded by any increase in core temperature. Although our data broadly support the previous findings in terms of magnitude of a core temperature change preceding a hot flush, the number of hot flushes preceded by an increase was less (51%) compared with previous research (65%).¹³ Given the current theory that an elevation in core temperature is the trigger for menopausal hot flushes, it may be fair to assume that the majority of women should experience a hot flush only when core temperature increases beyond a “set” temperature change (ie, $0.03\text{--}0.05^{\circ}\text{C}$ ^{7,11,13,31}). However, our data do not support this hypothesis as only half of the hot flushes were preceded by an increase in core temperature. Therefore, to explore the theory in more detail, we attempted to passively increase core temperature by at least 0.03°C using mild heating, to “provoke” a hot flush. We observed that not all women experienced a hot flush during mild heating, and that only 76% of the hot flushes that occurred were preceded by an increase in core temperature. On average, the increase in core temperature 20 minutes preceding a hot flush during mild heating was actually larger ($\sim 0.15^{\circ}\text{C}$) relative to the increase in core temperature preceding a spontaneous hot flush ($\sim 0.03^{\circ}\text{C}$), even when correcting for a time lag in gut temperature readings. Clearly, the larger increase in core temperature before the hot flushes during passive heating is due to the background thermoregulatory load. Of note, there were multiple segments of data where core temperature increased by at least $\sim 0.15^{\circ}\text{C}$ that did not culminate in a hot flush, demonstrating that the increase in core temperature with passive heating itself was unlikely to be the primary trigger for the hot flush. Consistent with this thought, the larger increase in core temperature before a hot flush during mild heating supports the argument that a 0.03°C increase,

which is “physiologically” very small and occurs frequently throughout everyday life in all postmenopausal women,¹⁵ is not an absolute trigger for a hot flush. Collectively, these findings suggest that core temperature does not consistently increase before hot flushes, and the magnitude of the elevation in core temperature before a hot flush is unlikely to be the trigger of the thermoregulatory event.

In the current study, we also revisited whether symptomatic postmenopausal women have a lower core temperature threshold for sweating.¹⁴ This previous observation is intriguing, given that a lower threshold for sweating is usually associated with enhanced thermoregulatory function and higher levels of fitness^{32,33}; during the follicular phase of the menstrual cycle, which is characterized by high levels of estrogen, the temperature threshold for sweating is lower^{32,34}; and aging (especially older age) is associated with an increased core temperature threshold for sweating.^{35,36} We used an abrupt and exponential rise in sweating, relative to core temperature, as the gold standard marker for the sweating threshold.²⁹ We observed similar temperature thresholds for the onset of sweating in response to whole-body passive heating between symptomatic postmenopausal and young premenopausal women, but the amount of sweat produced after the threshold (slope) was significantly less in symptomatic postmenopausal women. This is the first time the sweating thresholds have been compared across these age ranges in females. Despite not evaluating a group of asymptomatic postmenopausal women to compare temperature sweating thresholds with the symptomatic postmenopausal women, we would not expect asymptomatic postmenopausal women to have a lower sweating threshold relative to the assessed premenopausal women. If anything that threshold would be higher given known effects of aging increasing the core temperature sweating threshold.^{35,36}

A novel aspect of the current study was that we also compared cutaneous vasodilatory thresholds between symptomatic postmenopausal and premenopausal women. The core temperature threshold for cutaneous vasodilation were also similar, but the increase in forearm skin blood flow after that threshold (slope) was significantly less in symptomatic postmenopausal women compared with premenopausal women. Taken together, the data suggest that postmenopausal women who experience hot flushes produce less sweat and vasodilate less as heat stress progresses, potentially suggesting that they are less efficient at heat dissipation. However, we recognize that those responses may be simply an effect of age, independent of hot flush symptomatic status.

It is conceivable that a hot flush as a thermoregulatory event can occur without the trigger being an increase in core temperature, given the evidence of elevations in sweating and skin blood flow in the absence of alterations in core temperature via neural or non-neural/local mechanisms.³⁷ We show that the thermoregulatory series of events preceding a hot flush does not follow a typical temporal pattern that would be observed with increases in core temperature during passive heating.³⁷ Moreover, an elevation in efferent skin sympathetic

nerve activity before and during a hot flush (ie, a neural response), which has been described previously,⁸ likely provokes or contributes to the magnitude of increases in sweating and skin blood flow in the absence of a core temperature increase. The finding of increased brainstem activity before hot flushes¹⁶ may support the notion that hot flush responses are independent of the typical thermoregulatory control centres (eg, preoptic hypothalamic regions). Another alternative, albeit speculative, explanation is that the core temperature threshold for sweating during the menopausal transition is not fixed, but transiently changes, such that a hot flush is triggered by the temporary shifting of the sweating threshold set-point below the individual’s core temperature.³⁸ Under conditions of a fever, the temperature threshold for the onset of sweating initially increases, thereby reducing the incidence of sweating, and later, this threshold decreases, provoking profound sweating.³⁹ Exogenous pyrogens from bacteria generally cause fever; yet, circulating endogenous pyrogens (cytokines) have been associated with menopausal hot flushes,⁴⁰ and the interaction between such cytokines and temperature thresholds in symptomatic postmenopausal women warrants further investigation.

Implications

Collectively, these data provide important insight for symptomatic women and healthcare professionals in understanding the triggers for hot flushes. A small increase in core temperature is unlikely to induce a hot flush; therefore, recommendations for women to avoid conditions that may increase their core temperatures and to avoid/not perform exercise should be reconsidered. We have shown previously that exercise training/increased fitness reduces the frequency and severity of hot flushes, along with a lowering of the temperature thresholds for sweating and cutaneous vasodilation in symptomatic postmenopausal women.^{18,30} Exercise training improves sympathetic activity, vascular function, and sweat rate control in postmenopausal women, all of which may be implicated in the trigger for a hot flush.

CONCLUSIONS

We provide new evidence that menopausal hot flushes are not triggered by an increase in core body temperature. It is possible that a hot flush ensues due to underlying control mechanisms that are nonthermoregulatory in nature, or are thermoregulatory in nature and are triggered by a transient lowering of the core temperature threshold for the onset of sweating. These data provide important insight into the physiology of hot flushes and have important implications for lifestyle interventions as a potential treatment and management option for menopausal hot flushes.

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