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Physical Activity and Exercise for Hot Flashes: Trigger or Treatment?

Sarah Witkowski
Smith College, switkowski@smith.edu

Rose Evard
Smith College

Jacquelyn J. Rickson
Smith College

Quinn White
Smith College

Lynnette Leidy Sievert
University of Massachusetts Amherst

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Title: Physical Activity and Exercise for Hot Flashes: Trigger or Treatment?

Running Title: Physical Activity and Hot Flashes

Authors: Sarah Witkowski, PhD¹, Rose Evard¹, Jacquelyn J. Rickson, PhD¹, Quinn White¹, Lynnette Leidy Sievert, PhD²

Affiliations:

¹Department of Exercise & Sport Studies, Smith College, Northampton, MA

²Department of Anthropology, University of Massachusetts, Amherst, MA

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Corresponding Author:

Sarah Witkowski, PhD
102 Lower College La
Smith College
Northampton, MA
413-585-4555
switkowski@smith.edu

Abstract

Importance and Objective: Hot flashes (HFs) are a prevalent feature of menopause. Hot flashes can be bothersome and affect quality of life. However, HFs have also been associated with the risk for cardiovascular disease. Therefore, providing current evidence on the effect of therapies to reduce HFs can help patients and providers with decision-making. This review provides details on the scientific evidence to date related to the effect of physical activity and exercise to alter the HF experience in women.

Methods: The PubMed database was searched between June 2020 and June 2022 for currently available evidence regarding the relation between physical activity and exercise and HFs. Our analysis included randomized control trials on exercise training, epidemiological studies, and studies evaluating acute exercise on the self-reported and objectively-measured HF experience in addition to systematic reviews on the topic published as of June 2022.

Discussion and Conclusion: The majority of evidence from randomized control trials indicate that aerobic and resistance exercise training lead to a decrease in subjectively-experienced HFs. The limited available studies on acute exercise indicate that a bout of moderate intensity exercise may decrease objectively measured and self-reported HFs but acute increases in physical activity intensity above accustomed levels may influence subjective HF experience. Some evidence suggests that for those with depression, habitual physical activity may be an effective way to reduce HF symptoms. Weighing the available evidence, for people who experience HFs, engaging in regular moderate intensity physical activity, including aerobic and resistance exercise, may be an effective therapy to reduce HFs and women should be counseled on the benefits of regular, moderate exercise. However, significant gaps in knowledge remain about the optimal exercise prescription, effectiveness for a diverse population, meaning of differences between objective and subjective experience, and mechanisms that lead to changes in HFs.

Key Words: Menopause, Physical Activity, Exercise, Hot Flashes

Introduction:

Hot flashes (HFs) are sudden-onset heat dissipation events often characterized by a sensation of warmth, sweating, and increased heart rate. Approximately 80% of women will experience HFs around menopause, and they can persist for up to 10 years or longer.¹⁻³ Menopausal HFs are often bothersome and can negatively affect quality of life⁴⁻⁶ and are now recognized as a potential marker of cardiovascular disease (CVD) risk.⁷⁻¹⁰ Therefore, understanding the HF experience in order to develop effective interventions and recommendations is important for women's health through midlife and beyond.

Despite exciting developments in the understanding of the etiology of HFs, the exact causes remain unclear, and many therapies are only modestly effective. The MsFLASH study identified vasomotor symptoms (VMS) as the top priority menopausal symptom for treatment.¹¹ For some women, non-pharmaceutical options such as physical activity (PA) may be a preferred option to reduce HFs.^{12,13} However, the effectiveness of PA and exercise to change the HF experience is not well understood. This is likely due to a variety of factors, including differences in HF and PA measurement methodologies between studies, lack of knowledge on the impact of acute

exercise on the HF experience, and an overall limited number of research studies on the topic. Therefore, the objective of this review is to organize and present evidence on the efficacy of PA and exercise to influence the HF experience in order to better inform practitioners in their discussions with patients.

Methods:

PubMed was searched between June 2020 and June 2022 for primary sources. Search terms included: Menopause, Menopause symptoms, Hot Flashes/Hot Flushes, Vasomotor symptoms, Physical Activity, Exercise, and Acute exercise. Abstracts were reviewed to determine relevance. All studies published as of June 2022 were considered. References of selected sources were reviewed for appropriate articles not captured through the database search. To be included, studies needed to examine PA and/or exercise in relation to HFs and be published in English. Hot flashes were the primary response variable of interest, but studies that grouped HFs into broader categories — namely VMS or somatic symptoms—were included and, in applicable situations, will be referred to by the broad category. Investigations solely on night sweats were omitted as were studies about general menopausal symptoms wherein data on HFs were not specifically detailed. All study designs were accepted, and studies were separated by movement type for analysis (i.e., acute exercise, PA, or long-term exercise training). In total, 23 primary research studies were included in this analysis. One Cochrane review of randomized control trials on the topic has been published¹⁴, which was also reviewed.

Discussion

Pathophysiology of Hot Flashes

The precise etiology of HFs is still undetermined but HFs involve the thermoregulatory responses that maintain thermal homeostasis. Hot flashes induce heat dissipation, as evidenced by peripheral vasodilation and sweating¹⁵ following HF onset. The preoptic area of the hypothalamus (POA) controls thermoregulation¹⁶ and is hypothesized to become dysregulated due to menopausal estrogen withdrawal. KNDy neurons (named according to their co-expression of kisspeptin, neurokinin B and dynorphin) in the arcuate hypothalamus are currently believed to be along the neuronal pathway of HF generation as they have projections into the POA.^{17,18} Downstream effectors of neural activation are cutaneous vessels and sweat glands, as sympathetic cholinergic activation initiates a heat dissipation response through increased skin blood flow and sweating.^{19,20}

Thermal homeostasis is represented by the thermoneutral zone (TNZ) or the range of internal core temperature (T_c) between shivering and sweating. T_c above the upper boundary will induce sweating and T_c below the lower boundary will induce shivering. It is hypothesized that menopause leads to a reduction in the TNZ.²¹⁻²³ Understanding how thermoregulation and neuroendocrinology are involved in HFs will help to develop better treatments for menopausal HFs.

What are possible mechanisms by which hot flashes, physical activity and exercise are related? Hot flashes and PA both engage heat dissipation and share two main components of thermoregulation, changes in skin blood flow (cutaneous vasodilation) and sweating. These two

processes together transfer and dissipate body heat. Skin blood flow is controlled by reflex and local control mechanisms. Acute dynamic exercise causes initial sympathetic skin vasoconstriction as blood is distributed to working muscle.^{24,25} Continued exercise causes further increases in body temperature and active cholinergic vasodilation.²⁶ Increased body temperature also stimulates the POA to send sympathetic cholinergic signals to sweat glands to increase sweat production. The combined effect of these responses is a heat dissipation response to an acute exercise-induced increase in thermal load.

Acute exercise is defined as a single bout of increased physical activity that is planned with the objective to maintain or improve physical health or fitness. Acute exercise has been considered a potential trigger of HFs via an increase in Tc above the sweating threshold. Freedman and Krell²¹ conducted the first study to determine whether the threshold for sweating and shivering differed between women who did and did not subjectively experience HFs. In this study, women exercised to increase Tc until they experienced a HF or until one hour elapsed. All 12 of the symptomatic women had HFs during the acute exercise and the 8 asymptomatic women did not. Thus, this study became the basis for the hypothesis that acute exercise triggers HFs in symptomatic women by increasing Tc beyond the sweating threshold.

However, the hypothesis that HFs are preceded by an increase in Tc²⁷ has been questioned. Jones et al.²⁸ showed that only 51% of spontaneous HFs were preceded by an increase in Tc and, during mild heating to provoke HFs, 76% were preceded by an increase in Tc. Freedman et al.^{27,29} also showed that HFs could be preceded by decreases and no change in Tc; therefore, an increase in Tc is sufficient but not necessary to elicit a HF. While these studies did not evaluate exercise-induced HFs, it is possible that acute exercise may not consistently trigger HFs via increased Tc.

Exercise training and habitual PA lead to improved thermoregulation, such that active vasodilation and sweating occur at a lower body temperature^{30,31} and vasodilation is increased to a greater extent compared to untrained individuals.³⁰⁻³² The overall effect is that exercise training leads to a more efficient heat dissipation response. Jones et al.²⁸ reported that in response to heat stress, the skin blood flow and sweat responses were lower in women who reported HFs compared with asymptomatic women - an indication that efficiency of heat dissipation was worse in symptomatic women. However, Bailey et al.³³ showed that 16 weeks of exercise training improved thermoregulatory control in postmenopausal symptomatic women via lowering of sweat rate and blood flow thresholds and improving sweating sensitivity (increase in sweating per degree temperature increase). The same group³⁴ also reported lower vasodilation and sweating during a HF after training. Together, these data support an improvement in the capacity to cool the body during a HF via exercise training.

Assessment of Physical Activity, Exercise, and Hot Flashes

Physical activity is a behavior defined as body movement produced by skeletal muscle that results in energy expenditure above rest.³⁵ Physical activity can be separated into occupational, leisure time, and activities of daily living. Exercise is one type of PA that is planned and performed for the purpose of fitness or health. Physical activity, exercise, and HFs can be

recorded in two different ways: objectively and subjectively. For an in-depth discussion of PA reporting, the authors recommend Ainsworth et al.³⁶ Briefly, data collected objectively are produced from monitors, such as accelerometers and heart rate monitors, affixed to a person. Subjective data are participant self-reports of their own activity, commonly through surveys or diaries. A major limitation of self-reports is that they rely upon the participant's own memory, which can be unreliable. Furthermore, social desirability can result in overreporting of PA³⁷, and lighter-intensity activity is often underreported.³⁸ The method used to record PA ultimately depends on the questions the study is asking.

Hot flashes are most commonly documented through participant subjective self-reports, either through diaries or surveys. HF frequency and severity are often recorded, as together they compose the HF experience. Well-established menopausal surveys tend to combine HF symptoms with other VMS, including night sweats. As with self-reported PA, HFs recorded through surveys have the potential to be over- or underreported due to recall bias. Hot flashes can also be objectively documented through sternal skin conductance (SSC) monitors. For a discussion of SSC monitors, the authors recommend Sievert.³⁹ For SSC measurement, electrodes are placed on either side of the sternum to record sweat rate through skin conductance. Skin conductance that increases $>2\mu\text{mho}$ within 30 seconds is deemed an objective HF. In addition to the objective recording, participants can self-report a HF via button-push on the monitor, which allows for simultaneous objective and subjective reporting. Few studies to date have taken advantage of objective HF reporting when examining PA and exercise.

Does exercise training change the HF experience?

The strongest evidence of the effectiveness of exercise to reduce HFs comes from randomized control trials (RCTs) employing supervised exercise interventions.^{34,40–47} All intervention studies to date have assessed the subjective experience of HFs with diaries and questionnaires (e.g. Greene Climacteric Scale); none have used objective measures of HFs. Evidence from intervention trials in which participants were prescribed regular exercise show mixed results for the effect of exercise on HFs in peri- and postmenopausal people. All of the studies informing this question are RCTs, except for one preference trial.³⁴ The majority of studies employed aerobic exercise^{34,42–45,48}, while some utilized combination aerobic and resistance exercise,^{40,46,47} with one using resistance exercise exclusively.⁴¹ The majority of studies prescribed moderate intensity exercise^{34,40,42–46,48}, however interventions differed in program supervision, program length and sessions per week (details below). These studies varied in the level of HF or VMS frequency, intensity or both required for inclusion, with most requiring daily HF or VMS^{34,41,43–45,48} while others had no HF or VMS criteria for inclusion.^{40,42,46,47} The studies also differed in the design of their control groups; the control groups received counseling,⁴⁰ a placebo pill,⁴³ a stretching intervention⁴⁵, some form of educational health-related information^{41,42, 46, 56}, or simply were not treated.^{32, 33, 40,44,47} Confounders relevant to these RCTs include age, racial background, body mass index, and other sociodemographic characteristics. Most RCTs compared the descriptive statistics between the control and treatment groups to establish that they were not significantly different, but several studies adjusted for multiple covariates.^{39,43,56}

The majority of intervention studies (6 of 9) show an effect of exercise training to reduce subjective HF experience or VMS.^{33,34,40–43,48} In a 12-week aerobics intervention, both exercise groups (one incorporated nutrition education) reported significantly fewer HFs after the intervention compared to control and nutrition education only groups.⁴² In a 16-week aerobics preference trial, HF frequency and severity significantly decreased in the exercise group only.³⁴ In one study, a 4-month program of moderate intensity walking (3 sessions/week, 60minutes/session) or yoga (2 sessions/week, 90 minutes/session) showed significant reductions in VMS with both types of exercise compared to the control group.⁴⁸ Luoto et al.⁴³ showed in a 6-month program that 4 days/week (50 minutes/session) of moderate aerobic exercise significantly decreased self-reported nighttime HFs but not daytime HFs. Recent data from the FLAMENCO project, a RCT that employed a 16-week multicomponent exercise training program of aerobic exercise, balance training and resistance exercise (3days/week, 60 minutes/session), in women aged 45-60, revealed that self-reported VMS decreased to a greater extent in the exercise group compared with the control group, accounting for body mass index and adherence to the Mediterranean diet.⁴⁰ The only trial evaluating resistance training was a 16-week RCT in which investigators found that moderate and severe HF occurrence was significantly reduced after 3 weeks in the exercise group, and, by the completion of the intervention, decreased by 43.6% in the exercise group. The control group had no significant changes.⁴¹ Overall, the results from these studies suggest that aerobic and resistance exercise training lead to a decrease in number of subjectively-experienced HFs among women at midlife.

Two randomized controlled trials showed no significant effect of exercise training on the HF experience. The KEEPS trial⁴⁴ was a 12-week supervised intervention in which participants in the exercise group exercised 3 days/week at a moderate intensity. At the end of the intervention, there were small decreases in VMS frequency and bother but these reductions were similar to the control group, adjusting for age, race, and baseline VMS frequency, body mass index, fitness level, activity behavior, and health status. Daley et al.⁴⁵ implemented a 6-month unsupervised moderate exercise intervention and showed no change in HFs or night sweats for the exercise group at the end of the trial, but the lack of supervision means this result may be explained by a lack of engagement in the recommended activity. Finally, Aiello et al.⁴⁶ conducted a 12-month moderate intensity semi-supervised intervention in overweight postmenopausal women. The exercise group goal was 45 minutes of moderate intensity exercise 5 days per week. This study reported outcomes at 3, 6, 9, and 12 months. Researchers showed that, while the odds of reporting HFs was lower in the exercise group compared to controls at each time period, the differences were not significant. The odds of reporting moderate to severe HFs, however, were greater in the exercise group as the study progressed (9 and 12 months). Of note, this trial included people who reported low levels of moderate to severe HFs at baseline (11 out of 87) and only 17-20% of the participants reported any symptom at baseline.⁴⁶

While the above evidence demonstrates that most studies have shown an effect of exercise training to reduce HF experience, there remain several limitations and questions. First, all of these studies only use subjective reporting of VMS. While the subjective report remains a critical

aspect of how women feel, there are issues concerning recall with diaries and other subjective report tools. Through objective monitoring of physiological HFs, it has been shown that the subjective and objective HF experience are not always congruent.^{39,49} Second, most of these studies are in postmenopausal women. Hot flashes are most likely during the late perimenopausal and early post-menopausal stages of reproductive aging⁵⁰ and HF experience may differ by menopausal stage; for example, postmenopausal women who have experienced HFs for years may not report high levels of bother. Third, these studies represent different durations of exercise training (12 weeks to 12 months) and most did not report inter-term assessments. A variety of physiological adaptations occur with exercise training – all with different time scales – and it is not clear how long adaptations related to HF experience may take. Finally, the potential mechanisms of exercise training-induced adaptations that may change HF experience in women have only begun to be evaluated.³³ Therefore, overall, there is accumulating evidence that exercise training can improve the self-reported experience of VMS but more investigation is necessary to understand whether objective measures are similarly affected and the potential factors that contribute to or cause training-induced changes in HF experience.

Does acute exercise impact the HF experience?

Exercise training adaptations occur due to repeated bouts of acute exercise. Therefore, understanding whether acute exercise itself changes the HF experience is an important consideration. A bout of dynamic exercise that engages about 50% of skeletal muscle mass leads to metabolic heat production that causes changes in the core to body surface temperature ratio, increased sweat rate, and movement of blood toward the skin.^{51,52} Therefore, while the stimulus is different, the thermoregulatory response is similar between exercise and HFs.

To date, there have been three studies specifically evaluating the relationship between acute physical activity and HF experience using objective monitoring. Elavsky et al.⁵³ measured objective and subjective HFs for 24 hours after a controlled laboratory bout of 30-minute, moderate intensity treadmill exercise in women aged 40-60 years. They showed that a moderate-intensity bout decreased both subjective (-26%) and objective (-23%) daytime HFs in the 24 hours following exercise. They also reported that performing a greater amount of moderate PA than usual was related to more subjective HFs in women with lower fitness. Slavin, et al.⁵⁴ showed a decrease in self-reported VMS following an aerobics class. Other studies showed the opposite. Thurston, et al.⁵⁵ showed a slightly greater odds of a measured HF after self-reported physical exertion within 30 minutes (OR, 1.49;95% CI, 0.99-2.25; p=0.05) and HFs were more likely after a perceived effort of PA that was ≥ 2 out of a 5-point scale (OR, 1.51; 95%CI, 1.18-1.95, p=0.001). Gibson et al.⁵⁶ tested whether acute objectively-measured increases in PA within 10 minutes prior to a HF were related to subjectively reported and objectively measured HF over 48 hours. Researchers showed that the likelihood of subjectively reporting HFs without objectively measured corroboration was modestly higher (OR 1.04, 95% CI: 1.00-1.10, p=0.02) following acute increases in PA compared with mean daytime PA. Acute increases in PA were not associated with increased frequency of HFs that were objectively reported, subjectively reported, or objectively measured without self-reported corroboration. Additionally, women with higher levels of depression and anxiety had the highest level of reporting HF without objective corroboration following an increase in PA. While not entirely

consistent, these findings show that moderate intensity exercise may decrease objectively measured and self-reported HFs, but acute variations in PA intensity, depression and anxiety may influence subjective HF reporting. These studies highlight the importance of measuring objective and subjective HF and PA to improve our understanding of these relationships.

Does habitual physical activity impact the HF experience?

Tracking PA over time allows assessment of how changes in PA impact HF experience. Only one intervention study to date has been designed with the intent to examine increases in general PA and symptom changes in menopausal women. Using an at-home study that distributed PA recommendations through either personalized recommendation or printed general suggestions, McAndrew et al.⁵⁷ reported that increased PA was related to lower reporting of physical and psychosocial symptoms when adjusting for age, stress level and body mass index. Notably, this relationship was found to be mediated by exercise self-efficacy, defined as the belief in one's capacity to exercise. No relations were found for VMS specifically, and all data were self-reported. Meanwhile, one cohort study surveyed peri-menopausal women with and without depression every six months for thirty-six months⁵⁸. In the women with depression, VMS symptoms improved as PA increased over time. Further, maintaining high PA was associated with lower risk of VMS over time. In non-depressive women, investigators only found an indication that highly-active women had increased risk of VMS.⁵⁸ Therefore, increasing PA may be particularly important for decreasing self-reported VMS in women with depression, a population that has higher reporting of HFs⁵⁹⁻⁶¹ and risk for CVD.^{62,63} This suggests that the experience of depression could act as a confounder in studies on the relationship between PA and the HF experience.

Cross-sectional surveys can also lend supportive evidence as to whether altering PA behavior impacts the HF experience. All cross-sectional surveys to date assess PA and HF symptoms through self-reported methods (e.g., the Menopause Rating Scale (MRS) and the International Physical Activity Questionnaire (IPAQ)). A study of postmenopausal women utilizing the MRS and IPAQ found no significant relationship between PA and VMS (including daily HFs); however, energy expenditure was inversely correlated with VMS, though the correlation was noted to be "weak."⁶⁴ Ivarsson et al.⁶⁵ questioned participants about exercise activity and also found that women with greater than 2 hours/week of exercise had less severe VMS than women who exercised less. Using self-report IPAQ and MRS questionnaires, Dabrowska-Galas et al.⁶⁶ found that women with higher levels of PA at work had significantly lower levels of severe VMS. Additionally, when comparing inactive and moderately active women, active women had significantly fewer symptoms consisting of sweating or hot flushes, cardiac issues, sleeping disorders, or joint and muscle issues, across all severity levels. A study of perimenopausal women that employed the Menopause-specific Quality of Life (MENQOL) survey and short-form IPAQ did not find any association between PA and VMS symptoms.⁶⁷ Overall, these cross-sectional studies do not provide consistent support for a beneficial effect of PA on HF experience. However, they do suggest that PA can influence a variety of menopausal symptoms in beneficial ways.

Future Directions

This analysis also reveals that many unknowns remain about the efficacy of PA to mediate the HF experience. For example, it is unclear whether the effect is different in peri- versus postmenopausal women or whether this effect varies over time. The majority of the studies described only evaluated postmenopausal women and, if perimenopausal women were included, the effects were not evaluated separately. Importantly, women of different racial and ethnic backgrounds experience HFs differently. For example, VMS are most prevalent, bothersome, and have the longest duration in Black women and not reported as often in Asian women^{3,68,69} Additionally, mental health status may influence the effect of PA on HF experience. Consequently, it will be essential to determine whether exercise and PA have similar effects across different populations. The effect of exercise training on HF experience may be due to increases in efficiency of cooling. If exercise training reduces the subjective HF experience through a more efficient cooling response, then bother may also be reduced; however, this hypothesis remains to be tested. Finally, the prescription for exercise, including frequency, duration, and intensity, is unclear. Most RCT studies employed moderate PA, and there is some evidence that very high amounts of PA may lead to more symptom reporting.^{58,67,70} That said, whether high amounts of PA influence objective HFs or whether lighter intensities of exercise or PA are effective in reducing HFs has not been evaluated.

Conclusion:

Our analysis of available data from randomized controlled trial interventions involving exercise training, studies evaluating the effect of acute exercise, and studies evaluating PA indicate that: 1) moderate intensity exercise training can reduce subjective reporting of HFs, 2) a moderate-intensity acute bout of exercise can decrease objectively-measured and self-reported HFs, and 3) engaging in habitual PA may be a method of reducing HF symptoms in women with depression. Therefore, for people who experience HFs, engaging in regular moderate intensity PA may reduce HFs. Considering the known health benefits of habitual PA on cardiovascular health, its importance for healthy aging and wellness, in addition to the conclusions from our analysis, midlife women experiencing HFs should be counseled on the benefits of regular moderate exercise.

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