MEDDOCS Open Access Publisher

Environmental Sciences: Open Access

Open Access | Research Article

Peripheral Thermoregulatory Compensation During Acute Heat Exposure in Heat-Vulnerable Adults: Physiological Responses Consistent with Non-Adrenergic, Non-Cholinergic Pathway Involvement

Emmanuel Kairania[1]*; Ainembabazi Onesimas[2]; Tweheyo Ronald[2]

[1]Department of Human Anatomy, Faculty of Health Sciences, Busitema University, Uganda.

[2]Faculty of Health Sciences, Busitema University, Uganda.

***Corresponding Author(s): Emmanuel Kairania**

Department of Human Anatomy, Faculty of Health Sciences, Busitema University, Uganda.

Email: kairaniaemma@gmail.com

Received: July 23, 2026

Accepted: Aug 12, 2026

Published Online: Aug 19, 2026

Journal: Environmental Sciences: Open Access

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Heat stress; Thermoregulation; NANC pathways.

Abstract

Background: Maintenance of thermal homeostasis during heat exposure depends on coordinated autonomic, vascular, and sudomotor responses. Although adrenergic and cholinergic pathways are recognized as principal regulators of heat dissipation, accumulating evidence suggests that Non-Adrenergic, Non-Cholinergic (NANC) mediators, including prostaglandins and histamine, may also contribute to peripheral thermoregulatory control. However, their physiological contribution during acute heat stress in heat-vulnerable adults remains poorly characterized.

Objective: To investigate whether pharmacological modulation of prostaglandin- and histamine-associated pathways alters peripheral thermoregulatory responses during controlled heat exposure.

Methods: Six heat-vulnerable adults (24–41 years) completed a repeated-measures crossover study under three experimental conditions: control, cyclooxygenase inhibition using ibuprofen (400 mg), and H1-receptor antagonism using cetirizine (10 mg). Participants underwent standardized heat exposure (35°C; 50–60% relative humidity) combined with moderate treadmill exercise. Core temperature, mean skin temperature, heart rate, and sweat rate were measured throughout baseline, exercise, and recovery. Data were analyzed using repeated-measures ANOVA with Bonferroni-adjusted comparisons and partial eta squared (η^2p).

Results: Heat exposure significantly increased skin temperature and sweat rate (both $P<0.01$). Ibuprofen was associated with the greatest attenuation of sweating and the largest increase in core temperature, whereas cetirizine produced moderate impairment of peripheral heat dis-

Cite this article: Kairania E, Onesimas A, Ronald T. Peripheral Thermoregulatory Compensation During Acute Heat Exposure in Heat-Vulnerable Adults: Physiological Responses Consistent with Non-Adrenergic, Non-Cholinergic Pathway Involvement. Environ Sci Open Access. 2026; 1(2): 1009.

sipation. Large physiological effect sizes were observed for sweat rate (η^2p=0.88) and skin temperature (η^2p=0.70). These findings indicate preserved core temperature through enhanced peripheral thermoeffector activation despite pharmacological modulation.

Conclusions: This pilot study provides preliminary physiological evidence that prostaglandin- and histamine-associated pathways contribute to peripheral thermoregulatory compensation during acute heat exposure. Although direct NANC activity was not measured, the observed physiological responses are consistent with a contributory role of these pathways in human heat dissipation and support further mechanistic investigations integrating molecular biomarkers with physiological measurements.

Introduction

Background

Climate change has substantially increased the frequency, intensity, and duration of extreme heat events worldwide, resulting in a growing burden of heat-related illness, reduced workforce productivity, and increased cardiovascular morbidity. Individuals with impaired thermoregulatory capacity—including older adults, sedentary individuals, outdoor workers, and those with chronic cardiometabolic conditions—are disproportionately vulnerable to environmental heat exposure. Consequently, understanding the physiological mechanisms that preserve thermal homeostasis has become an important priority in environmental physiology, occupational medicine, and climate-health research [1-9].

Human thermoregulation depends on coordinated interactions between central neural control and peripheral thermoeffector responses that balance metabolic heat production with environmental heat exchange. During heat exposure, effective dissipation of body heat relies primarily on cutaneous vasodilation and eccrine sweating, which increase convective, radiative, and evaporative heat loss. Failure of these responses results in progressive thermal strain, cardiovascular instability, dehydration, and increased susceptibility to exertional heat illness and heat stroke [1-5,9-18].

Classical models of human thermoregulation emphasize sympathetic adrenergic and cholinergic pathways as the principal mediators of peripheral heat dissipation. However, growing experimental evidence suggests that Non-Adrenergic, Non-Cholinergic (NANC) mechanisms also contribute to regulation of cutaneous vascular conductance and sudomotor activity. Among these mediators, prostaglandins and histamine have attracted considerable interest because of their vasoactive, inflammatory, and neuromodulatory actions that influence skin blood flow independently of classical autonomic signaling [19,20].

Experimental and clinical studies indicate that prostaglandin E_2 participates in hypothalamic thermosensitivity, vascular regulation, and thermal homeostasis, whereas histamine contributes to endothelial function, microvascular regulation, and local vasodilatory responses that facilitate heat exchange. Despite these observations, the integrated physiological contribution of these pathways during acute exercise-induced heat stress in humans remains incompletely understood [21,22].

This knowledge gap is particularly relevant as climate-related heat exposure increasingly affects occupational and community populations worldwide. Improved understanding of peripheral thermoregulatory compensation may facilitate development of physiological biomarkers for identifying individuals at increased risk of heat intolerance and may inform future occupational heat-health guidelines, personalized heat-risk assessment, and climate adaptation strategies [23].

Because direct manipulation of the complete NANC system is neither feasible nor ethically appropriate in humans, pharmacological modulation of prostaglandin synthesis and histamine H_1 receptors provides a pragmatic experimental approach for exploring physiological responses consistent with altered NANC activity. Accordingly, this pilot repeated-measures crossover study used ibuprofen and cetirizine as physiological probes to investigate whether modulation of these pathways alters peripheral thermoregulatory responses during standardized exercise-induced heat stress [20,21,24,25].

Study objective

The primary objective of this study was to investigate the contribution of prostaglandin- and histamine-associated pathways to peripheral thermoregulatory responses during acute heat exposure in heat-vulnerable adults by comparing physiological responses under control conditions and following pharmacological modulation using ibuprofen and cetirizine.

Hypothesis

We hypothesized that pharmacological modulation of prostaglandin- and histamine-associated pathways would attenuate peripheral heat dissipation, reduce sweating efficiency, alter skin temperature responses, and increase physiological thermal strain during standardized exercise-induced heat exposure.

Materials and methods

Study design

This pilot study employed a repeated-measures, randomized crossover experimental design to investigate thermoregulatory responses during acute heat exposure under three physiological conditions: (i) control (no pharmacological intervention), (ii) prostaglandin pathway inhibition using ibuprofen, and (iii) histamine pathway inhibition using cetirizine. Each participant completed all experimental conditions in a randomized order, allowing each individual to serve as his or her own control. This approach minimized interindividual physiological variability and increased the sensitivity for detecting within-subject changes in thermoregulatory responses.

The primary objective was to determine whether pharmacological inhibition of prostaglandin- and histamine-associated pathways altered peripheral thermoeffector responses during acute heat stress. Secondary objectives included evaluation of cardiovascular responses and exploration of physiological signatures consistent with Non-Adrenergic, Non-Cholinergic (NANC) involvement in heat dissipation.

The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for observational studies and repeated-measures human physiological investigations.

Study setting

Experimental testing was conducted under controlled laboratory conditions in an environmental chamber maintained at an ambient temperature of 35°C with a relative humidity of 50–

60%, conditions selected to reproduce moderate environmental heat stress while ensuring participant safety. All testing sessions were performed at approximately the same time of day to minimize circadian influences on thermoregulatory function.

Participants attended three separate experimental sessions, each separated by a minimum washout period of 72 hours to minimize potential carry-over effects from previous interventions.

Participants

Six apparently healthy adults (four males and two females; age range 24–41 years) identified as being at increased risk of heat intolerance based on lifestyle-related characteristics, including sedentary behaviour and reduced exercise tolerance, were recruited using convenience sampling.

Inclusion criteria

Participants were eligible if they:

- were between 18 and 45 years of age;
- were able to complete moderate treadmill exercise;
- had no history of cardiovascular disease;
- were free from acute febrile illness;
- had no known allergy or contraindication to ibuprofen or cetirizine.

Exclusion criteria

Participants were excluded if they:

- were current smokers;
- were taking medications known to influence thermoregulation or cardiovascular function;
- had chronic inflammatory or metabolic disease;
- were pregnant;
- had experienced recent heat illness or hospitalization.

All participants received written and verbal explanations of the study procedures before providing written informed consent.

Because this investigation was designed as an exploratory physiological pilot study, no formal a priori sample size calculation was performed. The repeated-measures crossover design was selected to maximize statistical efficiency despite the small cohort by reducing between-subject variability and improving the precision of within-subject comparisons.

Randomization and experimental conditions

Participants completed three experimental conditions in randomized order using a computer-generated allocation sequence.

The experimental conditions were:

1. **Control condition** (no pharmacological intervention);
2. **Prostaglandin pathway inhibition**, achieved through administration of **ibuprofen 400 mg orally**;
3. **Histamine pathway inhibition**, achieved through administration of **cetirizine 10 mg orally**.

Ibuprofen and cetirizine were administered 90 minutes before heat exposure, consistent with their established pharmacokinetic profiles to ensure adequate systemic drug availability during physiological testing.

The pharmacological agents were used as physiological probes to transiently attenuate prostaglandin- and histamine-associated signaling pathways rather than as selective inhibitors of all NANC mechanisms. Consequently, interpretations regarding NANC involvement remain exploratory and should not be interpreted as evidence of direct mechanistic causation(26–29).

Experimental heat exposure protocol

Participants underwent standardized heat exposure while performing moderate treadmill exercise within the environmental chamber.

Each experimental session consisted of:

- 15-minute seated baseline rest
- 30-minute moderate-intensity treadmill exercise
- 20-minute seated recovery period

Exercise intensity was standardized across sessions using a moderate workload designed to induce physiologically relevant thermoregulatory activation while minimizing excessive cardiovascular strain.

Participants were instructed to:

- avoid strenuous physical activity for 24 hours before testing;
- abstain from caffeine and alcohol for 24 hours;
- maintain normal hydration;
- avoid non-prescription medications before each experimental session.

Compliance with these instructions was confirmed verbally before testing commenced(30–37).

Physiological measurements

Core body temperature

Core body temperature was monitored continuously using validated tympanic thermometry. Measurements were obtained at baseline and throughout exercise and recovery according to standardized procedures commonly employed in human heat-stress investigations.

Mean skin temperature

Mean skin temperature was measured continuously using calibrated surface thermistors positioned at standardized anatomical sites. These measurements provided an index of peripheral heat dissipation through cutaneous vasodilation.

Sweat rate

Whole-body sweat rate was estimated using changes in nude body mass measured immediately before and after exercise. Body mass differences were corrected for fluid intake during testing and expressed as sweat loss over the exercise period.

Cardiovascular measurements

Heart rate was monitored continuously using wearable telemetry throughout baseline, exercise, and recovery.

Systolic and diastolic blood pressures were measured using automated sphygmomanometry at standardized time points during each experimental phase.

Measures to reduce bias

Several measures were implemented to minimize potential sources of bias.

The repeated-measures crossover design allowed each participant to serve as his or her own control, substantially reducing interindividual variability. Experimental sessions were conducted under identical environmental conditions using standardized exercise protocols and measurement procedures. Testing was performed at similar times of day to minimize circadian influences on thermoregulatory responses.

Randomization of intervention order reduced potential sequence effects, while standardized participant instructions regarding hydration, physical activity, caffeine, alcohol consumption, and medication use minimized behavioural confounding. Data collection procedures and physiological measurements were performed using the same equipment and standardized protocols across all experimental sessions.

Despite these precautions, residual confounding cannot be completely excluded owing to the exploratory nature of the pilot study and the modest sample size [30-32,38-42].

Statistical analysis

Statistical analyses were performed using **IBM SPSS Statistics version 26.0** (IBM Corp., Armonk, NY, USA).

Continuous variables are presented as **mean ± standard error of the mean (SEM)** unless otherwise specified.

Repeated-measures analysis of variance (RM-ANOVA) was used to examine changes across experimental conditions and study phases while accounting for within-subject correlations.

Where statistically significant main effects were observed, Bonferroni-adjusted post hoc comparisons were performed to account for multiple testing.

Effect sizes were quantified using **partial eta squared (η^2p)** and interpreted according to conventional thresholds:

- small (0.01)
- moderate (0.06)
- large (≥0.14)

Pearson correlation coefficients were calculated to examine relationships among thermoregulatory variables.

Statistical significance was accepted at **$P<0.05$**.

Given the exploratory pilot nature of the study and limited sample size, emphasis was placed on interpretation of effect sizes alongside statistical significance to facilitate assessment of physiological relevance [43-52].

Missing data

No participants withdrew from the study, and complete physiological data were obtained for all six participants across all experimental sessions. Consequently, no missing observations required imputation or statistical adjustment, and analyses were performed using complete-case data.

Ethical considerations

The study was conducted in accordance with the ethical principles of the **Declaration of Helsinki** for research involving human participants.

Ethical approval was obtained through the institutional ethical review framework of **Selinus University of Science and Literature, Italy**.

Written informed consent was obtained from all participants before enrolment.

Participant confidentiality was maintained by assigning unique study identification codes, and all data were securely stored with access restricted to the research team.

Results

Participant characteristics

Six participants (four males and two females; age range, 24–41 years) completed all three experimental sessions, including the control, prostaglandin blockade, and histamine blockade conditions. No participant withdrew from the study, and no adverse events or protocol deviations occurred during heat exposure or exercise testing. Baseline physiological variables, including core body temperature, mean skin temperature, heart rate, and blood pressure, were comparable across experimental sessions, indicating consistent pre-exposure physiological status.

Core body temperature

Core body temperature increased progressively from baseline to exercise in all experimental conditions and remained mildly elevated during the recovery period (Figure 3). Participants receiving prostaglandin blockade exhibited the greatest increase in core temperature during exercise, whereas histamine blockade produced an intermediate response compared with the control condition.

Repeated-measures ANOVA demonstrated no statistically significant overall differences in core body temperature across experimental phases:

$F(2,10)=0.57$, $P=0.584$, $\eta^2p=0.10$.

Although these differences did not reach statistical significance, the observed effect size suggested a modest physiological influence of pharmacological blockade on thermal regulation. The preservation of core temperature despite environmental heat stress indicates effective activation of compensatory thermoregulatory mechanisms throughout the experimental protocol.

Mean skin temperature

Mean skin temperature increased significantly during exercise under all experimental conditions, reflecting activation of peripheral heat dissipation mechanisms (Figure 1).

Repeated-measures ANOVA demonstrated a significant effect of experimental phase on skin temperature:

$F(2,10)=11.74$, $P=0.002$, $\eta^2p=0.70$.

Participants receiving ibuprofen demonstrated attenuated increases in skin temperature relative to the control condition, whereas histamine blockade produced intermediate responses. These findings indicate reduced peripheral thermoeffector activation following pharmacological modulation of prostaglandin-

and histamine-associated pathways.

The large effect size ($\eta^2p=0.70$) indicates substantial physiological modulation of peripheral vascular heat dissipation despite the modest sample size.

Sweat rate

Sweat rate increased significantly during exercise and remained elevated during the recovery phase across all experimental conditions (Figure 2).

A significant main effect of experimental phase was observed:

$F(2,10)=35.23$, $P<0.001$, $\eta^2p=0.88$.

The greatest attenuation of sweating occurred following prostaglandin blockade, while histamine blockade resulted in a moderate reduction compared with the control condition. The exceptionally large effect size ($\eta^2p=0.88$) indicates marked physiological differences in sudomotor responses associated with pharmacological modulation.

Pearson correlation analysis demonstrated an inverse relationship between sweat rate and indices of thermal strain, with reduced sweating associated with greater heat retention during exercise. This relationship supports the importance of sweating as a primary thermoeffector response during acute environmental heat exposure.

Integrated thermophysiological responses

Comparison of central and peripheral thermal responses demonstrated distinct patterns of thermoregulatory compensation. Despite relatively modest increases in core body temperature, substantial increases in skin temperature and sweat production were observed during exercise, indicating preferential activation of peripheral heat-loss mechanisms.

Participants exposed to prostaglandin blockade consistently demonstrated reduced peripheral heat dissipation compared with the control condition, while histamine blockade produced less pronounced attenuation. These observations suggest that prostaglandin- and histamine-associated pathways may contribute to peripheral thermoeffector responses during acute heat stress.

Summary of physiological effect sizes

Among all physiological variables examined, sweat rate demonstrated the largest effect size ($\eta^2p=0.88$), followed by skin temperature ($\eta^2p=0.70$) and core body temperature ($\eta^2p=0.10$).

Although statistically significant differences were not observed for every outcome, particularly core temperature, the magnitude of the observed effect sizes indicates physiologically meaningful alterations in peripheral thermoregulatory responses. These findings support the interpretation that pharmacological modulation primarily influenced peripheral heat-loss mechanisms rather than central thermal regulation during the relatively short period of heat exposure.

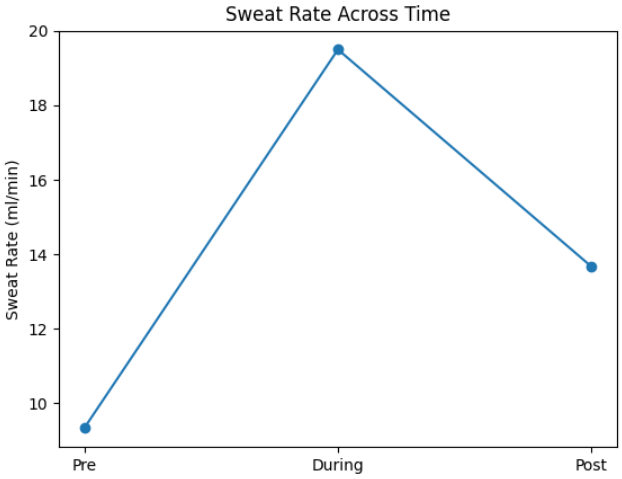

Figure 2: Sweat rate responses during acute heat exposure. Mean (± SD) sweat rate across baseline, exercise, and recovery phases under the three experimental conditions. Sweat production increased significantly during exercise ($P<0.001$), with the greatest attenuation observed following prostaglandin pathway inhibition. These findings demonstrate the dominant contribution of sudomotor activation to peripheral heat dissipation.

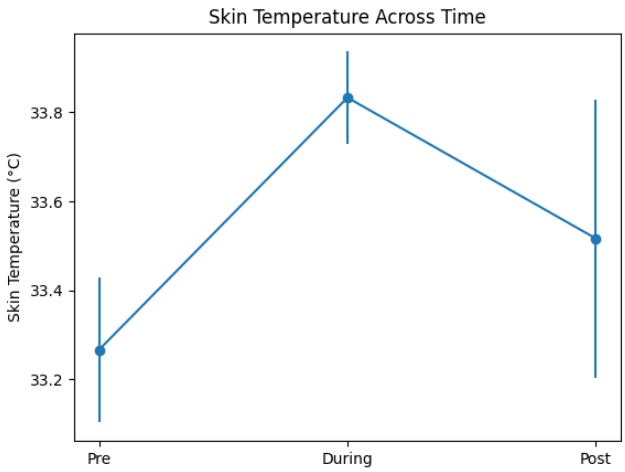

Figure 1: Mean skin temperature responses during acute heat exposure. Mean (± SD) skin temperature during baseline, exercise, and recovery under the control, prostaglandin blockade (ibuprofen), and histamine blockade (cetirizine) conditions. Skin temperature increased significantly during exercise ($P=0.002$), consistent with activation of peripheral heat-loss mechanisms. Attenuated responses following pharmacological modulation are consistent with reduced peripheral thermoeffector activity.

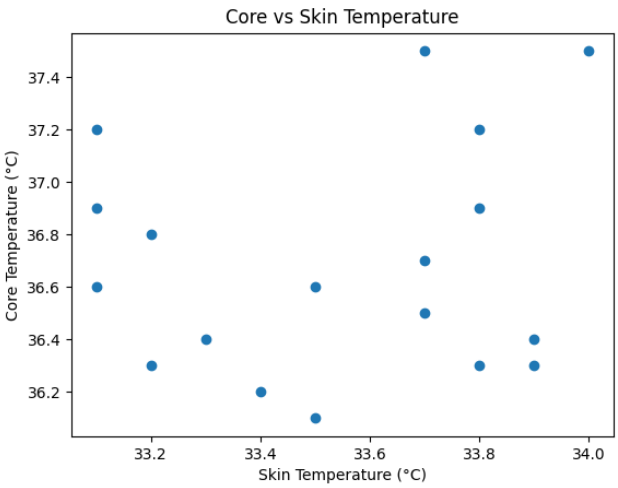

Figure 3: Relationship between peripheral and core thermoregulation during acute heat exposure. Scatter plot illustrating the relationship between mean skin temperature and core body temperature across all experimental phases. Despite marked increases in peripheral temperature, core body temperature remained relatively stable, demonstrating effective short-term thermoregulatory compensation during environmental heat stress.

Discussion

The present study investigated peripheral thermoregulatory responses during acute heat exposure using pharmacological modulation of prostaglandin- and histamine-associated pathways as physiological probes of Non-Adrenergic, Non-Cholinergic (NANC) mechanisms. The principal findings were that (i) peripheral heat-loss responses, particularly sweating and increases in skin temperature, were significantly activated during exercise in a hot environment; (ii) pharmacological modulation with ibuprofen and cetirizine attenuated these peripheral thermoeffector responses, with the greatest reduction observed following prostaglandin pathway inhibition; and (iii) core body temperature remained relatively stable despite reductions in peripheral heat dissipation, suggesting effective short-term physiological compensation during acute heat exposure. Collectively, these findings provide preliminary physiological evidence consistent with a contributory role of prostaglandin- and histamine-associated pathways in peripheral thermoregulatory adaptation [27,31,32,34,44,45,53-57].

Peripheral thermoregulatory compensation during heat stress

Maintenance of thermal homeostasis during environmental heat exposure depends on the coordinated activation of cutaneous vasodilation and eccrine sweating, which facilitate convective and evaporative heat loss while limiting excessive increases in core body temperature. Consistent with established models of human thermoregulation, participants demonstrated significant increases in mean skin temperature and sweat rate during exercise, reflecting effective recruitment of peripheral heat-loss mechanisms in response to increased thermal load. These observations agree with previous physiological studies showing that sweating and cutaneous vasodilation constitute the principal effector mechanisms for maintaining thermal balance during exercise in the heat.

An important observation was that relatively stable core body temperature was maintained despite substantial changes in peripheral thermoeffector activity. This dissociation between central and peripheral thermal responses highlights the efficiency of compensatory physiological mechanisms that preferentially enhance peripheral heat dissipation before substantial elevations in core temperature occur. Such findings reinforce contemporary concepts of integrated thermoregulatory control, in which peripheral vascular and sudomotor adjustments provide an early protective response against thermal strain [39,58-66].

Evidence consistent with NANC-mediated thermoregulation

Classical physiological models emphasize sympathetic adrenergic and cholinergic pathways as the primary regulators of heat dissipation. However, increasing experimental evidence indicates that vasoactive mediators, including prostaglandins, histamine, nitric oxide, Vasoactive Intestinal Peptide (VIP), and Calcitonin Gene-Related Peptide (CGRP), may contribute to local vascular regulation and sweating through complementary non-adrenergic, non-cholinergic mechanisms.

In the present study, pharmacological modulation of prostaglandin- and histamine-associated pathways resulted in attenuation of sweating and skin temperature responses, with prostaglandin inhibition producing the greatest reduction in peripheral heat-loss capacity. Although ibuprofen and cetirizine do not selectively inhibit all NANC pathways, their use as pharmacological probes provides indirect physiological evidence that these signaling systems may contribute to thermoeffector activation during acute heat stress.

Given the exploratory design and limited sample size, these observations should be interpreted cautiously. The present findings do not establish direct mechanistic involvement of prostaglandins or histamine in human thermoregulation but are consistent with emerging evidence that multiple vasoactive mediators interact to optimize peripheral heat dissipation under thermal stress. Future mechanistic studies incorporating direct measurements of prostaglandins, histamine, nitric oxide, CGRP, and skin blood flow will be required to confirm these physiological pathways [21,64,67-81].

Physiological importance of sweating responses

Among all measured variables, sweat rate demonstrated the largest physiological effect size ($\eta^2p=0.88$), suggesting that sudomotor function represented the most responsive thermoeffector during acute heat exposure. Although the sample size limited statistical power for some outcomes, the magnitude of the observed effect supports the biological importance of sweating as the primary mechanism of evaporative heat loss.

Reduced sweating during prostaglandin blockade was accompanied by modestly greater thermal strain, suggesting that even partial impairment of peripheral thermoeffector function may decrease heat-loss efficiency. These findings are consistent with previous investigations demonstrating that impaired sweating contributes to increased susceptibility to heat intolerance, particularly among individuals with reduced thermoregulatory reserve, older adults, and workers exposed to prolonged environmental heat [19,82-90].

Implications for heat vulnerability and climate adaptation

The physiological responses observed in this study have broader relevance in the context of global climate change and increasing occupational heat exposure. Heat-related illness is becoming an increasingly important public health challenge, particularly among outdoor workers, older adults, and individuals with obesity, sedentary lifestyles, or chronic cardiometabolic disease. Identification of early physiological indicators of impaired heat dissipation is therefore critical for improving prevention strategies and reducing heat-related morbidity.

Although exploratory, the present findings suggest that peripheral thermoeffector responses, particularly sweating efficiency and skin temperature regulation, may represent sensitive physiological markers of early heat strain before clinically significant elevations in core body temperature occur. Future validation of these responses, together with molecular biomarkers of vascular function, could contribute to individualized heat-risk assessment, occupational surveillance programmes, and precision heat-health interventions in climate-vulnerable populations [62,88,91-96].

Translational significance

The translational implications of this work extend beyond experimental physiology. As environmental temperatures continue to rise, improved understanding of peripheral thermoregulatory function may inform occupational health guidelines, athletic heat-management protocols, and community-based climate adaptation strategies. Integration of wearable physiological monitoring technologies with objective measures of

peripheral heat dissipation may facilitate early identification of individuals at increased risk of heat-related illness and improve the effectiveness of preventive interventions.

The present findings therefore provide a physiological framework for future translational research investigating wearable biosensors, personalized heat-risk prediction, and biomarker-guided approaches to heat-health resilience [21,64,65,76-79,82,91,97-101].

Strengths

Several strengths enhance the scientific value of this investigation. First, the repeated-measures crossover design minimized interindividual variability by allowing each participant to serve as his or her own control. Second, standardized environmental conditions and exercise protocols improved internal validity and reproducibility. Third, continuous physiological monitoring enabled detailed characterization of dynamic thermoregulatory responses throughout baseline, exercise, and recovery. Finally, pharmacological modulation provided an ethically acceptable and clinically relevant approach for exploring physiological pathways potentially associated with NANC-mediated thermoregulation.

Limitations

Several limitations should be acknowledged when interpreting the present findings. First, this was an exploratory pilot study involving only six participants, limiting statistical power and generalizability. Consequently, the observed findings should be regarded as preliminary and hypothesis-generating rather than definitive.

Second, ibuprofen and cetirizine served as broad pharmacological probes rather than selective inhibitors of NANC signaling. Although these agents provide indirect evidence regarding prostaglandin- and histamine-associated pathways, they do not permit definitive attribution of the observed physiological responses to specific molecular mechanisms.

Third, direct assessment of cutaneous vascular function using laser Doppler flowmetry, venous occlusion plethysmography, or similar techniques was not performed. Likewise, circulating or tissue biomarkers of prostaglandins, histamine, nitric oxide, vasoactive intestinal peptide, or calcitonin gene-related peptide were not quantified. Integration of physiological measurements with molecular biomarkers will be essential for confirming the mechanistic basis of the observed responses.

Finally, the relatively short duration of heat exposure was designed to ensure participant safety and may not fully replicate the prolonged environmental or occupational heat stress experienced by climate-exposed populations. Future investigations should include larger and more diverse cohorts, longer exposure periods, direct vascular measurements, and comprehensive biomarker profiling to better characterize NANC-mediated thermoregulatory adaptation.

Future directions

Future research should expand these preliminary findings through adequately powered randomized crossover studies incorporating direct assessment of skin blood flow, endothelial function, sweat gland activity, and circulating vasoactive mediators. Simultaneous measurement of prostaglandins, histamine, nitric oxide metabolites, CGRP, and VIP would allow more precise characterization of the molecular pathways contributing to peripheral heat dissipation.

Integration of wearable physiological sensors with biochemical biomarkers may facilitate development of precision approaches for early heat-risk detection in occupational, athletic, military, and community settings. Such investigations will be increasingly important as climate change intensifies the frequency, duration, and severity of environmental heat exposure worldwide.

Conclusion

This pilot repeated-measures crossover study provides preliminary physiological evidence consistent with a contributory role of prostaglandin- and histamine-associated pathways in peripheral thermoregulatory compensation during acute heat exposure. Pharmacological modulation of these pathways attenuated sweating and skin temperature responses while core body temperature remained relatively stable, indicating that peripheral heat-loss mechanisms effectively compensated for increased thermal load during short-term exercise in the heat.

Although the study was not designed to establish causal molecular mechanisms, the observed physiological patterns support the concept that Non-Adrenergic, Non-Cholinergic (NANC)-associated signaling may complement classical autonomic pathways in facilitating human heat dissipation. These findings expand current understanding of integrative thermoregulatory physiology and provide a foundation for future mechanistic investigations incorporating direct assessment of vascular function and molecular biomarkers.

Given the increasing frequency and intensity of environmental heat exposure associated with climate change, improved understanding of peripheral thermoregulatory adaptation has important implications for occupational health, environmental physiology, and heat-risk management. Larger, adequately powered studies integrating physiological monitoring with biomarker profiling are warranted to validate these preliminary findings and determine their potential application in personalized heat-health assessment and prevention strategies.

Clinical perspective

Effective maintenance of thermal homeostasis depends on rapid activation of peripheral heat-loss mechanisms before clinically significant elevations in core body temperature occur. The present findings suggest that changes in sweating efficiency and skin temperature may provide sensitive physiological indicators of early heat strain. Although exploratory, these observations support further investigation of peripheral thermoeffector function as a potential physiological marker for identifying individuals at increased risk of heat-related illness.

Translational perspective

Rising global temperatures and increasing occupational heat exposure present growing challenges to human health and productivity. Improved understanding of peripheral thermoregulatory physiology may contribute to the development of individualized heat-risk assessment strategies, wearable physiological monitoring systems, and evidence-based occupational heat management programmes. The present findings provide preliminary physiological evidence supporting future translational research aimed at improving heat resilience among climate-vulnerable populations.

Author declarations

Data availability statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request. Data will be shared in accordance with institutional ethical requirements and participant confidentiality agreements.

Ethics statement

The study was conducted in accordance with the principles of the Declaration of Helsinki for research involving human participants. Ethical approval was obtained through the institutional ethical review framework of Selinus University of Science and Literature, Italy. All participants provided written informed consent prior to enrolment after receiving detailed information regarding the study procedures, potential risks, and anticipated benefits.

Author contributions

Emmanuel Kairania: Conceptualization, methodology, investigation, formal analysis, data curation, visualization, writing—original draft, writing—review and editing, supervision, **Ainembabazi Onesimas:** Investigation, data interpretation, writing—review and editing; **Tweheyo Ronald:** Methodology, data interpretation, writing—review and editing. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The work was undertaken as part of doctoral research and subsequently informed ongoing postdoctoral investigations into human thermoregulation and heat physiology.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgements

The authors sincerely thank all study participants for their time and commitment. We also acknowledge the support of the Faculty of Health Sciences, Busitema University, for providing an academic environment that facilitated this work. Appreciation is extended to colleagues who contributed valuable discussions during the design and interpretation of the study.

What is already known?

Peripheral heat dissipation is traditionally attributed to autonomic adrenergic and cholinergic pathways. Emerging evidence indicates that prostaglandins, histamine, and other locally acting vasoactive mediators may also participate in regulating cutaneous vasodilation and sweating, although their contribution during acute heat exposure remains incompletely understood.

What this study adds

Using a repeated-measures crossover design with pharmacological physiological probes, this study demonstrates that inhibition of prostaglandin- and histamine-associated pathways is accompanied by reduced sweating and altered peripheral thermoregulatory responses during controlled heat stress. These findings provide preliminary evidence supporting a contributory role of NANC-related mechanisms in human heat dissipation.

How this study might affect research, practice, or policy

As extreme heat events become increasingly common, identifying early physiological markers of impaired heat dissipation may improve occupational heat-risk assessment and climate-health adaptation strategies. If validated in larger cohorts, peripheral thermoeffector responses could contribute to individualized heat-vulnerability screening and wearable physiological monitoring systems.

References

1. Agrawal K, Bosviel R, Piccolo BD, Newman JW. Oral ibuprofen differentially affects plasma and sweat lipid mediator profiles in healthy adult males. Prostaglandins Other Lipid Mediat. 2018; 137.
2. Aitken WW, Brown SC, Comellas AP. Climate change and cardiovascular health. J Am Heart Assoc. 2022; 11.
3. Alahmad B, Khraishah H, Althalji K, Borchert W, Al-Mulla F, Koutrakis P. Connections between air pollution, climate change, and cardiovascular health. Can J Cardiol. 2023; 39: 9.
4. Amoadu M, Ansah EW, Sarfo JO, Hormenu T. Impact of climate change and heat stress on workers' health and productivity: A scoping review. J Clim Change Health. 2023; 12.
5. Amoadu M, Ansah EW, Sarfo JO, Hormenu T. Impact of climate change and heat stress on workers' health and productivity: A scoping review. J Clim Change Health. 2023; 12.
6. Balmain BN, Jay O, Morris NR, Shiino K, Stewart GM, Jayasinghe R, et al. Thermoeffector responses at a fixed rate of heat production in heart failure patients. Med Sci Sports Exerc. 2018; 50: 3.
7. Balmain BN, Sabapathy S, Louis M, Morris NR. Aging and thermoregulatory control: The clinical implications of exercising under heat stress in older individuals. Biomed Res Int. 2018; 2018.
8. Bennett LAT, Johnson JM, Stephens DP, Saad AR, Kellogg DL. Evidence for a role for vasoactive intestinal peptide in active vasodilatation in the cutaneous vasculature of humans. J Physiol. 2003; 552: 1.
9. Brozmanová A. Thermoregulation of skin blood flow. Cesk Fysiol. 2003; 52.
10. Burdon CA, Tagami K, Park J, Caldwell JN, Taylor NA. Does the skin of mildly hyperthermic individuals display local variations in thermosensitivity for the control of skin blood flow? Extrem Physiol Med. 2015; 4.
11. Charkoudian N. Skin blood flow in adult human thermoregulation: How it works, when it does not, and why. Mayo Clin Proc. 2003; 78: 603–612.
12. Charkoudian N. Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. J Appl Physiol. 2010; 109: 4.
13. Charkoudian N. Optimizing heat dissipation for every environment: The cool ability of the skin to locally regulate sweating. J Appl Physiol. 2010; 109: 5.
14. Charkoudian N. Human thermoregulation from the autonomic perspective. Auton Neurosci. 2016; 196.
15. Charkoudian N, Morrison SF. Physiology of thermoregulation: Central and peripheral mechanisms. In: Primer on the Autonomic Nervous System. 4th ed. 2022.

16. Cheuvront SN, Haymes EM. Thermoregulation and marathon running: Biological and environmental influences. Sports Med. 2001; 31: 10.

17. Crandall CG, Wilson TE, Kregel KC. Mechanisms and modulators of temperature regulation. J Appl Physiol. 2010; 109: 4.

18. De Vita A, Belmusto A, Di Perna F, Tremamunno S, De Matteis G, Franceschi F, et al. The impact of climate change and extreme weather conditions on cardiovascular health and acute cardiovascular diseases. J Clin Med. 2024; 13.

19. Havenith G, Taylor NAS. Limitations to thermoregulation and acclimatization challenge human adaptation to global warming. Int J Environ Res Public Health. 2015; 12: 7.

20. Emerson DM, Chen SC, Torres-McGehee TM, Pfeifer CE, Emerson CC, Davis JM. An acute naproxen dose does not affect core temperature or interleukin-6 during cycling in a hot environment. Sports Med Health Sci. 2021; 3: 4.

21. Emerson DM, Torres-McGehee TM, Davis JM, Chen SCL, Durstine JL, Pfeifer CE, et al. Effects of a 24-h naproxen dose on hydration and electrolyte measures during moderate-intensity cycling in the heat. FACETS. 2017; 2.

22. Esh CJ, Chrismas BCR, Mauger AR, Cherif A, Molphy J, Taylor L. The influence of environmental and core temperature on cyclooxygenase and PGE2 in healthy humans. Sci Rep. 2021; 11.

23. Falk B. Effects of thermal stress during rest and exercise in the paediatric population. Sports Med. 1998; 25: 4.

24. Fujii N, McGinn R, Halili L, Singh MS, Kondo N, Kenny GP. Cutaneous vascular and sweating responses to intradermal administration of ATP: A role for nitric oxide synthase and cyclooxygenase? J Physiol. 2015; 593: 11.

25. Fujii N, Nikawa T, Tsuji B, Kenny GP, Kondo N, Nishiyasu T. Wearing graduated compression stockings augments cutaneous vasodilation but not sweating during exercise in the heat. Physiol Rep. 2017; 5.

26. Fujii N, Paull G, Meade RD, McGinn R, Stapleton JM, Akbari P, et al. Do nitric oxide synthase and cyclooxygenase contribute to the heat loss responses in older males exercising in the heat? J Physiol. 2015; 593: 14.

27. Fujii N, Tanabe Y, Amano T, Watanabe K, Kondo N, Nishiyasu T, et al. Serum, interstitial and sweat ATP in humans exposed to heat stress: Insights into roles of ATP in the heat loss responses. Clin Physiol Funct Imaging. 2023; 43: 5.

28. Gagnon D, Romero SA, Cramer MN, Jay O, Crandall CG. Cardiac and thermal strain of elderly adults exposed to extreme heat and humidity with and without electric fan use. JAMA. 2016; 316: 9.

29. Giersch GEW, Charkoudian N. Regulation of body temperature and blood pressure in women: Mechanisms and implications for heat illness risk. Exp Physiol. 2025; 110: 2.

30. González-Alonso J, Kalsi KK. The ubiquitous ATP molecule: Could it be the elusive thermal mediator igniting skin perfusion and sweating in the heat-stressed human? J Physiol. 2015; 593: 11.

31. Gopathi P, Tiwari KH, Kalpana K. The effects of pre-exercise ice-slurry ingestion on thermoregulation and exercise performance of highly trained athletes: A scoping review. Int J Exerc Sci. 2023; 16.

32. Hailes WS, Cuddy JS, Cochrane K, Ruby BC. Thermoregulation during extended exercise in the heat: Comparisons of fluid volume and temperature. Wilderness Environ Med. 2016; 27.

33. Hanna EG, Tait PW. Limitations to thermoregulation and acclimatization challenge human adaptation to global warming. Int J Environ Res Public Health. 2015; 12.

34. Holowatz LA, Kenney WL. Mechanisms and modulators of temperature regulation: Peripheral mechanisms of thermoregulatory control of skin blood flow in aged humans. J Appl Physiol. 2010; 109.

35. Holowatz LA, Kenney WL. Peripheral mechanisms of thermoregulatory control of skin blood flow in aged humans. J Appl Physiol. 2010; 109.

36. Holzer P, Jocîc M, Peskar BA. Mediation by prostaglandins of the nitric oxide-induced neurogenic vasodilatation in rat skin. Br J Pharmacol. 1995; 116.

37. Hom LL, Lee ECH, Apicella JM, Wallace SD, Emmanuel H, Klau JF, et al. Eleven days of moderate exercise and heat exposure induces acclimation without significant HSP70 and apoptosis responses of lymphocytes in college-aged males. Cell Stress Chaperones. 2012; 17.

38. Hutchins KP, Borg DN, Bach AJE, Bon JJ, Minett GM, Stewart IB. Female (under) representation in exercise thermoregulation research. Sports Med Open. 2021; 7.

39. Ige-Elegbede J, Powell J, Pilkington P. A systematic review of the impacts of extreme heat on health and wellbeing in the United Kingdom. Cities Health. 2024; 8.

40. Ijima E, Kodera S, Hirata A, Hikage T, Matsumoto A, Ishitake T, et al. Excessive whole-body exposure to 28 GHz quasi-millimeter wave induces thermoregulation accompanied by a change in skin blood flow proportion in rats. Front Public Health. 2023; 11.

41. Inoue Y, Havenith G, Kenney WL, Loomis JL, Buskirk ER. Exercise- and methylcholine-induced sweating responses in older and younger men: Effect of heat acclimation and aerobic fitness. Int J Biometeorol. 1999; 42.

42. Iwahashi M, Hasegawa H. The gender differences in exercise performance and thermoregulatory responses to body cooling between exercises in a hot environment. Adv Exerc Sports Physiol. 2021; 27.

43. Jay O, Cramer MN. A new approach for comparing thermoregulatory responses of subjects with different body sizes. Temperature. 2015; 2.

44. Kamijo YI, Nose H. Heat illness during working and preventive considerations from body fluid homeostasis. Ind Health. 2006; 44.

45. Katznelson E, Cascio WE, Bernstein A, Chaudhary R, Al-Roub N, Liu CL, et al. Climate change and cardiovascular health: A systematic review. J Am Coll Cardiol. 2023; 81.

46. Katznelson E, Malkani K, Zhang R, Patel S. Impact of climate change on cardiovascular health. Curr Atheroscler Rep. 2024; 27.

47. Kazi DS, Katznelson E, Liu CL, Al-Roub NM, Chaudhary RS, Young DE, et al. Climate change and cardiovascular health: A systematic review. JAMA Cardiol. 2024; 9.

48. Kenny GP, Flouris AD. The human thermoregulatory system and its response to thermal stress. In: Protective Clothing: Managing Thermal Stress. 2014.

49. Kenny GP, Notley SR, Flouris AD, Grundstein A. Climate change and heat exposure: Impact on health in occupational and general populations. In: Exertional Heat Illness: A Clinical and Evidence-Based Guide. 2019.

50. Kenny GP, Poirier MP, Metsios GS, Boulay P, Dervis S, Friesen BJ, et al. Hyperthermia and cardiovascular strain during an extreme heat exposure in young versus older adults. Temperature. 2017; 4.

51. Keramidas ME, Kölegård R, Eiken O. Hypoxia gradually augments metabolic and thermoperceptual responsiveness to repeated whole-body cold stress in humans. Exp Physiol. 2020; 105.

52. Kondo N, Taylor NAS, Shibasaki M, Aoki K, Muhamed AMC, Taylor NA, et al. Thermoregulatory adaptation in humans and its modifying factors. Glob Environ Res. 2009; 13.

53. Kraning KK, Montain SJ. A computer simulation to predict the physiological effects of progressive dehydration. FASEB J. 1996; 10.

54. Kunda JJ, Gosling SN, Foody GM. The effects of extreme heat on human health in tropical Africa. Int J Biometeorol. 2024; 68.

55. Lahondère C. Recent advances in insect thermoregulation. J Exp Biol. 2023; 226.

56. Larose J, Boulay P, Sigal RJ, Wright HE, Kenny GP. Age-related decrements in heat dissipation during physical activity occur as early as the age of 40. PLoS One. 2013; 8.

57. Bennett LAT, Johnson JM, Stephens DP, Saad AR, Kellogg DL Jr. Evidence for a role for vasoactive intestinal peptide in active vasodilatation in the cutaneous vasculature of humans. J Physiol. 2003; 552.

58. Lenasi H, Šijanec J. The physiology of thermoregulation in exercise: A brief review. Eur Med J. 2023; 7.

59. Li J, Zhou Z, Wu Y, Zhao J, Duan H, Peng Y, et al. Heat acclimation defense against exertional heat stroke by improving the function of preoptic TRPV1 neurons. Theranostics. 2025; 15.

60. Li T, Wang Q, Cheng C. Effect of aging on cardiovascular responses to cold stress in humans. Frigid Zone Med. 2022; 2.

61. Lim CL. Fundamental concepts of human thermoregulation and adaptation to heat: A review in the context of global warming. Int J Environ Res Public Health. 2020; 17.

62. Lv T, Liu Q, Wang Y, Zhang P. Climate change and cardiovascular health: Environmental stressors, mechanistic insights, and clinical perspectives. Rev Cardiovasc Med. 2025; 26.

63. Mack G, Nishiyasu T, Shi X. Baroreceptor modulation of cutaneous vasodilator and sudomotor responses to thermal stress in humans. J Physiol. 1995; 483.

64. Malhi JK, McEvoy JW, Blumenthal RS, Jacobsen AP. Climate change and cardiovascular health: Recent updates and actions for healthcare. Am Heart J Plus. 2024; 45.

65. McLellan TM, Rhind SG, Bell DG. Body temperature in sedentary adults during moderate exercise: No effect from exercise the day before. Aviat Space Environ Med. 2002; 73.

66. Medow MS, Glover JL, Stewart JM. Nitric oxide and prostaglandin inhibition during acetylcholine-mediated cutaneous vasodilation in humans. Microcirculation. 2008; 15.

67. Mena CS. Impact of climate change on cardiovascular health outcomes. J Am Coll Cardiol. 2023; 81.

68. Millyard A, Layden JD, Pyne DB, Edwards AM, Bloxham SR. Impairments to thermoregulation in the elderly during heat exposure events. Gerontol Geriatr Med. 2020; 6.

69. Mündel T. Thermoregulatory sweating and evaporative heat loss during exercise: Is the whole greater than the sum of its parts? J Physiol. 2020; 598.

70. Mündel T, Gilmour S, Kruger M, Thomson J. Reliability of a 60-min treadmill running protocol in the heat: The journal Temperature toolbox. Temperature. 2023; 10.

71. Murage P, Hajat S, Macintyre HL, Leonardi GS, Ratwatte P, Wehling H, et al. Indicators to support local public health to reduce the impacts of heat on health. Environ Int. 2024; 183.

72. Namisnak LH, Haghayegh S, Khoshnevis S, Diller KR. Bioheat transfer basis of human thermoregulation: Principles and applications. J Heat Transf. 2022; 144.

73. Namisnak LH, Khoshnevis S, Diller KR. Interdependency of core temperature and glabrous skin blood flow in human thermoregulation function: A pilot study. J Biomech Eng. 2023; 145.

74. Navarro JS, Morrissey MC, Dierickx EE, Casa DJ. Physiological and thermoregulatory responses of body cooling during cycling in a hot environment. Med Sci Sports Exerc. 2022; 54.

75. Nazari S, Kourosh-Arami M, Komaki A, Hajizadeh S. Relative contribution of central and peripheral factors in superficial blood flow regulation following cold exposure. Physiol Pharmacol. 2020; 24.

76. Notley SR, Akerman AP, Meade RD, McGarr GW, Kenny GP. Exercise thermoregulation in prepubertal children: A brief methodological review. Med Sci Sports Exerc. 2020; 52.

77. Notley SR, Meade RD, D'Souza AW, Friesen BJ, Kenny GP. Heat loss is impaired in older men on the day after prolonged work in the heat. Med Sci Sports Exerc. 2018; 50.

78. Périard JD, Eijsvogels TMH, Daanen HAM. Exercise under heat stress: Thermoregulation, hydration, performance implications, and mitigation strategies. Physiol Rev. 2021; 101.

79. Rezaei Z, Hajizadeh S. Central and peripheral thermoregulatory responses to cold exposure: Involvement of sympathetic system, nitric oxide, and orexin. J Kerman Univ Med Sci. 2022; 29.

80. Rowsey LE, Kieffer JD, Speers-Roesch B. Temperature-dependent exercise recovery is not associated with behavioral thermoregulation in a salmonid fish. J Therm Biol. 2024; 123.

81. Schlader ZJ, Coleman GL, Sackett JR, Sarker S, Chapman CL, Johnson BD. Activation of autonomic thermoeffectors preceding the decision to behaviourally thermoregulate in resting humans. Exp Physiol. 2016; 101.

82. Schlader ZJ, Sarker S, Mündel T, Coleman GL, Chapman CL, Sackett JR, et al. Hemodynamic responses upon the initiation of thermoregulatory behavior in young healthy adults. Temperature. 2016; 3.

83. Schmidt MD, Notley SR, Meade RD, Akerman AP, Rutherford MM, Kenny GP. Revisiting regional variation in the age-related reduction in sweat rate during passive heat stress. Physiol Rep. 2022; 10.

84. Schoales C. Holistic perspectives on older persons' needs, Part 2: Skin, circulation, respiration, thermoregulation, and sex. Supporting Older Persons on Their Aging Journey. 2024.

85. Shefer VI, Talan MI. The effect of exercise training in a cold environment on thermoregulation in adult and aged C57BL/6J mice. Exp Gerontol. 1997; 32.

86. Siddiqui SA, Thiam S, Houndodjade C, Murage P, Bonell A. A systematic review and meta-analysis of the impact of environmental heat exposure on cardiovascular diseases, chronic respiratory diseases and diabetes mellitus in low- & middle-income countries. Environ Res. 2025; 282.

87. Šijanec J, Lenasi H. The physiology of thermoregulation in exercise. Southeast Eur Med J. 2023; 7.

88. Slesinski SC, Matthies-Wiesler F, Breitner-Busch S, Gussmann G, Schneider A. Social inequalities in exposure to heat stress and related adaptive capacity: A systematic review. Environ Res Lett. 2025; 20.

89. Tansey EA, Johnson CD. Recent advances in thermoregulation. Adv Physiol Educ. 2015; 39.

90. Tokizawa K, Lin CH, Nagashima K. Mechanisms of heat acclimation and tolerance induced by exercise training and heat exposure. J Phys Fit Sports Med. 2012; 1.

91. Toko H, Minamino T, Komuro I. Role of heat shock transcriptional factor 1 and heat shock proteins in cardiac hypertrophy. Trends Cardiovasc Med. 2008; 18: 52–57.

92. Tucker MA, Caldwell AR, Butts CL, Robinson FB, Reynebeau HC, Kavouras SA, et al. Effect of hypohydration on thermoregulatory responses in men with low and high body fat exercising in the heat. J Appl Physiol. 2017; 122: 142–149.

93. Vecellio DJ, Cottle RM, Wolf ST, Kenney WL. Critical environmental limits for human thermoregulation in the context of a changing climate. Exerc Sport Mov. 2023; 1: 78–86.

94. Veltmeijer MTW, Veeneman D, Bongers CCCW, Netea MG, Van Der Meer JW, Eijsvogels TMH, et al. The impact of central and peripheral cyclooxygenase enzyme inhibition on exercise-induced elevations in core body temperature. Int J Sports Physiol Perform. 2017; 12: 658–664.

95. Verdegaal ELJMM, Howarth GS, McWhorter TJ, Delesalle CJG. Thermoregulation during field exercise in horses using skin temperature monitoring. Animals. 2024; 14: 136.

96. Wee J, Tan XR, Gunther SH, Ihsan M, Leow MKS, Tan DSY, et al. Effects of medications on heat loss capacity in chronic disease patients: Health implications amidst global warming. Pharmacol Rev. 2023; 75: 1122–1160.

97. Wilkins BW, Chung LH, Tublitz NJ, Wong BJ, Minson CT. Mechanisms of vasoactive intestinal peptide-mediated vasodilation in human skin. J Appl Physiol. 2004; 97: 1291–1298.

98. Wong BJ. Which comes first in human temperature regulation: The physiological or the behavioural response? Exp Physiol. 2016; 101: 1213–1214.

99. Wong BJ, Hollowed CG. Current concepts of active vasodilation in human skin. Temperature. 2017; 4: 41–59.

100. Xu J, Wang Q, Anikeeva O, Zhu P, Bi P, Huang C. Effects of extreme heat on physiology, morbidity, and mortality under climate change: Mechanisms and clinical implications. BMJ. 2025; 391: e084675.

101. Zhang YQ. MicroRNA 142-3P may play as plasma marker for awake, unrestrained rats to heat stroke. Shock. 2020; 53: S63.