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A 3-D whole-body human thermoregulatory model to simulate extreme cold stress

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Prolonged exposure to Arctic-like conditions can lead to adverse physiological outcomes, significantly affecting the health, performance, and operational readiness of civilians and military personnel. In this study, we extended our previously developed, anatomically realistic, three-dimensional thermoregulatory virtual human model to more comprehensively predict changes in core body temperature and skin temperature of peripheral body regions (dorsum hand, fingertip, face, dorsum foot, and toe-tip) and the cheek under extreme cold-air temperatures down to -40.0°C and wind speeds ranging from 0.1 to $3.0\text{ m}\cdot\text{s}^{-1}$. To assess model performance, we computed the root mean square error (RMSE) between model predictions and experimental data as well as the fraction of model predictions that lie within two standard errors of the mean experimental data from eight cold-air exposure studies involving 75 unique subjects. Overall, we observed a reasonable agreement between model predictions and the experimental measurements, with average RMSEs of about 0.2°C for core body temperature, 0.5 to 1.8°C for mean skin, 1.6 to 2.7°C for fingertip, 1.2 to 3.5°C for toe-tip, and 2.1 to 2.7°C for cheek skin temperature. As such, the extended model can serve as a valuable tool to inform the development of guidelines to help mitigate the risk of cold-related injuries during prolonged exposures to extreme-cold environments.

Keywords Human thermoregulation, Bioheat transfer, Extreme cold-air exposure, Cold injury, Prolonged cold exposure, Dexterity loss

List of symbols

C	Forced convection coefficient (dimensionless)
c_p	Specific heat capacity ($\text{J}\cdot\text{kg}^{-1}\cdot\text{K}^{-1}$)
$c_{p,b}$	Specific heat capacity of blood ($\text{J}\cdot\text{kg}^{-1}\cdot\text{K}^{-1}$)
e	Forced convection exponent (dimensionless)
h_c	Convective heat-transfer coefficient ($\text{W}\cdot\text{m}^{-2}\cdot\text{K}^{-1}$)
i	Index for body segment (dimensionless)
k	Thermal conductivity ($\text{W}\cdot\text{m}^{-1}\cdot\text{K}^{-1}$)
N	Natural convection coefficient (dimensionless)
p_{bf}	Passing blood perfusion rate ($\text{m}^3\cdot\text{s}^{-1}\cdot\text{m}^{-3}$)
$\dot{Q}_{Act}$	Activity heat generation per unit volume of tissue ($\text{W}\cdot\text{m}^{-3}$)
$\dot{Q}_{met}$	Metabolic heat generation per unit volume of tissue ($\text{W}\cdot\text{m}^{-3}$)
$\dot{Q}_{Sh}$	Shivering heat generation per unit volume of tissue ($\text{W}\cdot\text{m}^{-3}$)
R^2	Coefficient of determination
t	Time (s)
T	Body temperature dependent on spatial location and time ($^{\circ}\text{C}$)
T_a	Arterial blood temperature ($^{\circ}\text{C}$)
T_{air}	Air temperature ($^{\circ}\text{C}$)
T_c	Core body temperature ($^{\circ}\text{C}$)
$T_{sk,i}$	Local skin temperature of the i th body segment ($^{\circ}\text{C}$)

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$T_{sk,m}$	Whole-body mean skin temperature (°C)
T_v	Venous blood temperature (°C)
U_{cl}^*	Local effective heat-transfer coefficient ($W \cdot m^{-2} \cdot K^{-1}$)
v_{air}	Wind speed ($m \cdot s^{-1}$)
$\dot{V}_{O_2}$	Rate of oxygen consumption per body unit mass ($mL \cdot min^{-1} \cdot kg^{-1}$)
β	Partial heat exchange coefficient for capillary perfusion (dimensionless)
χ	Passing blood flow heat exchange efficiency (dimensionless)
ρ	Tissue density ($kg \cdot m^{-3}$)
ρ_b	Blood density ($kg \cdot m^{-3}$)
ω_b	Blood perfusion rate ($m^3 \cdot s^{-1} \cdot m^{-3}$)
$\omega_{b,0}$	Baseline blood perfusion rate ($m^3 \cdot s^{-1} \cdot m^{-3}$)
ΔT_c	Change in core body temperature (°C)
$\Delta T_{sk,m}$	Change in mean skin temperature (°C)

Abbreviations

3-D	Three-dimensional
BMI	Body mass index
CIVD	Cold-induced vasodilation
FE	Finite element
MET	Metabolic equivalent of task
PBF	Passing blood flow
PBHE	Pennes bioheat transfer equation
RMSE	Root mean square error
SD	Standard deviation
SE	Standard error

Cold-weather injuries represent a concern to the U.S. military, significantly affecting the health, performance and operational readiness of Service members. During prolonged operations in Arctic-like conditions, exposure to cold and wet environments can lead to a decrease in operational effectiveness as well as cold injuries, including hypothermia and frostbite¹. For example, during deployment and training between July 2023 and June 2024, 456 U.S. Service members sustained at least one cold-weather injury, with 56.0% of these injuries attributed to frostbite². When the skin temperature drops due to cold exposure, the body's physiological response is to reduce warm blood flow to the peripheral regions, including the hands and feet, in order to preserve the vital organs. Over time, this decrease in blood flow leads to a reduction in the temperature at these regions and, eventually, to frostbite when the skin temperature falls below 0.0 °C^{3,4}.

Accurate quantification of the human body's thermal response during extreme-cold exposures can provide unique insights into injury risks and help develop measures to counter the threat of cold environments. However, achieving these goals by performing field studies in austere Arctic weather is challenging, and performing controlled laboratory studies with humans in extreme environmental conditions likely to lead to cold injuries is not ethical. When human experimentation is impractical or not possible, physics-based computational models that can represent the thermoregulatory responses of the human body with high fidelity and accurately predict the spatiotemporal temperature distribution throughout the body for a range of extreme environmental conditions offer a plausible alternative⁵.

Over the last decade, a few whole-body human thermoregulatory models have been proposed to provide insights into cold-injury risk in healthy men. Some approaches approximated the body's anatomy by representing it as concentric cylinders or spheres^{6–8}, which lack the needed spatial resolution to accurately predict the temperature variation at different regions of the body's periphery during cold exposure. For example, it is not clear how well these models can replicate the experimental results reported by Chen et al.⁹, who observed a 20.0 °C difference in temperature between the palm of the hand and the index finger during a 60-minute air exposure at 0.0 °C. In addition, by and large, these models were validated for only a limited number of conditions that covered very short exposure times (30 min)⁷ or only provided temperature values at a single point in time⁶, necessarily precluding a thorough assessment of the evolution of the predictions of skin and core body temperatures over time. In contrast, recent advances in computational modeling afforded the development of finite-element (FE), three-dimensional (3-D) thermoregulatory whole-body models that use high-fidelity human geometries with organ-level resolution, i.e., anatomically realistic models, for predicting the response of men to both hot and cold environments¹⁰. However, model validation was primarily focused on thermal-comfort conditions, with no assessments performed for air temperatures below 0.5 °C. Importantly, none of these models incorporated the necessary heat-transfer formulation to account for the spatial variation in blood temperature throughout the body and, in particular, within the body's extremities (arms and legs) required to accurately predict temperature changes during very cold exposures¹¹. This is evidenced by Gulati et al., who showed that without such a formulation the core body temperature can be underestimated by more than 1.5 °C during a 120-minute air exposure at 1.0 °C¹². Therefore, a key research gap includes the lack of well-validated thermoregulatory models that incorporate the physics required for extreme cold-air and -water exposures to predict population-average responses under such conditions.

Recently, our U.S. Department of Defense team developed a FE 3-D virtual human thermoregulatory model to predict the temperature distribution throughout the body in response to exertional and environmental heat stress, as well as environmental cold stress, within a unified framework^{12,13}. This model is a population-average

model based on an anatomically realistic description of a 50th percentile young, healthy U.S. male. The model accounts for the transfer of energy within the body and heat transfer between the body and the environment through convection, radiation, respiration, and perspiration, while considering the major thermoregulatory mechanisms of shivering, sweating, vasomotion, circadian-rhythm effects, and, more recently, cold-induced vasodilation (CIVD)¹⁴. The model is valid for both air and water exposures and includes a novel heat-transfer formulation capable of representing the spatial variation of blood temperature characteristic of extreme cold-stress exposures¹². The model takes environmental conditions, physical activity, and clothing as inputs and predicts the spatiotemporal distribution of temperatures in the entire virtual human as an output. Until now, the model had only been validated for temperatures between 0.0 and 45.0 °C. Here, our objective was to extend the virtual human model to predict the thermal responses to extreme cold-air exposures of an average U.S. male by updating the convection heat-transfer physics for the peripheral body regions and refining the phenomenological relationship of heat generation through shivering. Subsequently, we validated the model predictions for the hand, foot, face, and core body temperature for various clothing and environmental conditions, including air temperatures ranging from −40.0 to 12.0 °C, using eight experimental studies involving 75 unique subjects. As such, our study provides a novel approach to close a key research gap by extending and validating our previously developed virtual human model¹² for extreme cold-air exposures. With this model extension and validation, the 3-D virtual human thermoregulatory model is now capable of predicting the body's response to temperature exposures from −40.0 to 45.0 °C.

Materials and methods

Computational model

We recently developed and validated an anatomically realistic 3-D whole-body virtual human thermoregulatory model of an average 50th percentile U.S. male to simulate heat and cold stress across a wide range of ambient temperatures from 0.0 to 45.0 °C^{12–14}. Briefly, to develop the model, we acquired the geometry of an average 50th percentile U.S. male directly from Zygote Media Group (American Fork, UT), where the key anthropometric measurements included a weight of 83.8 kg, height of 175.0 cm, body-fat content of 15.0%, and body surface area of 1.9 m². The model accounts for the major metabolically active organs and biological tissues and considers the major heat-transfer and heat-exchange mechanisms within the human body and between the body and the environment as well as the thermoregulatory mechanisms that maintain and regulate the thermal balance of the body. To properly account for the different heat-transfer properties throughout the body, the model represents 12 different body segments, including the head, face, neck, shoulder, upper arm, lower arm, hand, thorax, abdomen, upper leg, lower leg, and foot. In this study, we calibrated the model's convective heat-transfer coefficients for the foot and cheek regions, refined the representation of heat generation due to shivering under extreme cold-air conditions, and extended the validation of the resulting model to assess its performance for exposures down to −40.0 °C.

Energy balance

As described in our previous works^{12,14}, we used a modified version of the Pennes bioheat transfer equation (PBHE)¹⁵ to compute the spatiotemporal temperature distribution within the human body by solving the macroscopic energy balance for the time-dependent temperature T . Briefly, the modified PBHE incorporates heat conduction between body segments, convective heat exchange between the passing blood flow (PBF) and the surrounding tissue prior to capillary perfusion, countercurrent heat transfer between venous and arterial blood, partial heat transfer between the capillaries, and heat sources to account for metabolic heat generation ($\dot{Q}_{met}$), heat generation due to physical activity ($\dot{Q}_{Act}$), and heat generation from shivering ($\dot{Q}_{Sh}$). Mathematically, we represented energy balance, as follows:

$$\underbrace{\rho c_p \frac{\partial T}{\partial t}}_{\text{Heat storage}} = \underbrace{\nabla \cdot k \nabla T}_{\text{Heat conduction}} + \underbrace{\chi \rho_b c_{p,b} (pbf) (T_a + T_v - 2T)}_{\text{Passing blood; flow; heat; exchange}} + \underbrace{\beta \rho_b c_{p,b} \dot{\omega}_b (T_a - T)}_{\text{Capillary blood perfusion}} + \underbrace{\dot{Q}_{met}}_{\text{Metabolic heat}} + \underbrace{\dot{Q}_{Act}}_{\text{Activity heat}} + \underbrace{\dot{Q}_{Sh}}_{\text{Shivering heat}} \quad (1)$$

where the parameters k , c_p , and ρ denote the thermal conductivity, specific heat, and density of biological tissue, respectively; $c_{p,b}$ and ρ_b represent the specific heat and density of blood, respectively; T_v and T_a denote the venous and arterial temperature of blood, respectively; and pbf denotes the passing blood perfusion rate. In addition, χ represents the heat-transfer efficiency of PBF; β represents a coefficient that accounts for the partial heat transfer occurring between the peripheral skin regions and the perfusing arterial blood; and $\dot{\omega}_b$ represents the blood perfusion rate. In what follows, we only describe the thermoregulatory mechanism of heat generation due to shivering and convective heat-transfer coefficients, which we refined to account for extreme-cold conditions. We refer the reader to Gulati et al.¹² for details regarding the other thermoregulatory mechanisms.

Heat generation due to shivering

We refined the correlation for predicting heat generation due to shivering $\dot{Q}_{Sh}$ for extreme cold-air exposures by including additional experimental data^{16–19} to account for the gradual increase in shivering for conditions

down to $-15.0\text{ }^{\circ}\text{C}$ (Supplementary Figure S1). (We could not identify experimental studies with the required shivering information for lower temperatures.) Briefly, as in our original formulation¹², the heat source $\dot{Q}_{Sh}$ due to shivering in Eq. (2) is represented by two terms: the first term captures the initial rapid rise in $\dot{Q}_{Sh}$ driven by the rate of change in whole-body mean skin temperature ($dT_{sk,m}/dt$) from its initial thermoneutral condition, while the second term reflects the gradual increase in $\dot{Q}_{Sh}$ as the whole-body mean skin temperature $T_{sk,m}$ decreases by up to $13.0\text{ }^{\circ}\text{C}$ during the period of the exposure (Supplementary Figure S1). Here, we updated the second term in Eq. (2), resulting in a larger coefficient for the quadratic component (1.28 versus 0.36), a much smaller coefficient for the linear component (0.92 versus 10.27), and the absence of a constant component to ensure that the curve passes through the origin when $\Delta T_{sk,m}$ is equal to zero. Accordingly, $\dot{Q}_{Sh}$ is now defined as follows:

$$\dot{Q}_{Sh} = \underbrace{7.60 - 109.80 \frac{dT_{sk,m}}{dt} - 1.90 \Delta T_{sk,m}}_{\text{Initial rise in shivering}} + \underbrace{1.28 \Delta T_{sk,m}^2 + 0.92 \Delta T_{sk,m}}_{\text{Gradual increase in shivering}} \quad (2)$$

We distributed the heat generated from shivering in Eq. (2) to the muscle tissues of the torso and the upper limbs as follows: 49.0% thorax, 26.0% legs, 22.0% abdomen, and 3.0% arms^{20,21}.

Calibration of convective heat-transfer coefficients

To better predict the skin temperature at the foot and cheek, we calibrated their convective heat-transfer coefficients h_c for air exposure. Namely, using the expression proposed by de Dear et al.²² and Wissler⁸ to estimate h_c in our original model^{12–14}, we calibrated the natural convection N_i and forced convection C_i coefficients for the i th body segment (foot or cheek, in this case) and the dimensionless forced convection exponent e_i , as follows:

$$h_c = \begin{cases} N_i(T_{sk,i} - T_{air})^{0.25}, & v_{air} < 0.2 \text{ m} \cdot \text{s}^{-1} \\ C_i(v_{air})^{e_i}, & 0.2 \text{ m} \cdot \text{s}^{-1} \leq v_{air} \leq 5.0 \text{ m} \cdot \text{s}^{-1} \end{cases} \quad (3)$$

where $T_{sk,i}$ denotes the local skin temperature and T_{air} and v_{air} represent the air temperature and wind speed, respectively. For water immersion, we used an average h_c value of $210.0 \text{ W} \cdot \text{m}^{-2} \cdot \text{K}^{-1}$ ²³. As outlined in our previous work¹², when simulating clothed conditions, we used the calibrated h_c to compute an “effective” local heat-transfer coefficient U_{ci}^* to account for the effects of convection and radiation between the skin and the external environment, as well as the effect of clothing.

Experimental studies

We used data from five experimental studies for model calibration and eight studies for independent model validation. Table 1 summarizes the five studies (*Studies C1–C5*) involving 43 unique subjects exposed to whole-body cold-stress conditions in air that we used for model calibration of the foot and toe as well as the cheek skin region^{10,24–27}. Table 2 summarizes the eight distinct studies (*Studies V1–V8*) involving 75 unique subjects exposed to whole-body cold-stress conditions in air that we used to validate the model predictions for core body temperature T_c , $T_{sk,m}$, as well as the cheek, hand, finger, foot, and toe skin temperatures^{17,19,28–32}. In addition, Supplementary Table S1 summarizes the anthropometric measurements of the subjects in the validation studies. We selected *Studies V1–V8* for model validation because they reported the evolution of skin temperature and core body temperature through time, including both mean and standard deviation values, for air temperatures ranging from -40.0 to $12.0\text{ }^{\circ}\text{C}$. We refer the reader to the original articles (*Studies V1–V5*, *V7*, *V8*) for additional information on the specific studies.

Study V6 in Table 2 pertains to a new cold-stress study that we conducted in an environmentally controlled chamber at the University of Connecticut. Prior to the study, we conducted a power analysis to estimate the sample size required for the cold-stress study to demonstrate equivalence between model-predicted and experimentally measured thermal responses. For this analysis, we selected skin temperature as the parameter of interest because it exhibits higher variability than core body temperature. To perform the power analysis, we estimated the prediction error, using the root mean square error (RMSE) between model-predicted and experimentally measured skin temperatures reported in a previous study³, and the mean and standard deviation of the measured skin temperature obtained from the literature^{33,34}. Then, we computed the sample size using the test for equivalence formula proposed by Chow et al.³⁵, which is based on the t-test. From this analysis, we found that a minimum of 12 subjects would be required to reject the null hypothesis (i.e., that the model-predicted skin temperatures significantly differ from the corresponding measured values) with an 80% power at a 5% significance level. We used a conservative sample size of 15 for this study.

We recruited 15 young (18–27 years old), healthy men (Supplementary Table S2) and exposed them for 2 h to an air temperature of $-10.0\text{ }^{\circ}\text{C}$, relative humidity of 40.0%, and wind speed of $1.0 \text{ m} \cdot \text{s}^{-1}$. We selected a $-10.0\text{ }^{\circ}\text{C}$ air temperature and $1.0 \text{ m} \cdot \text{s}^{-1}$ wind speed because they are representative of an Arctic-like, cold-exposure condition and because they fall within the operating range of the environmental chamber that could be stably maintained throughout the experiment. In addition, we set the relative humidity to 40.0% to minimize potential condensation-related interference with the chamber’s instrumentation. Subjects remained seated throughout the duration of the trial, while wearing a three-layer Arctic clothing ensemble (~ 3.6 clo), which

Study	Measurement Site	RMSE, °C (Fraction, %)	No. of Subjects	Duration (min)	Exposure Temp. (°C)	Wind Speed (m·s ⁻¹)	Relative Humidity (%)	Clothing (clo)	Source
C1	Rectum (10 cm) Whole-body mean Dorsum foot	0.1 (-) 0.9 (-) 0.5 (-)	5	60	10.0	0.1	40	0.57	24
C2	Rectum (10–12 cm) Whole-body mean Great toe-tip	0.2 (-) 1.7 (-) 0.8 (-)	7	120	7.5	0.1	80	0.57	25
C3	Rectum (10–12 cm) Great toe-tip	0.3 (58) 0.2 (100)	13	120	8.0	0.3	85	0.57	27
C4	Whole-body mean Cheek	0.8 (47) 2.3 (47)	12	30	-15.0	0.1	65	2.16	26
C5	Gastrointestinal tract Whole-body mean Cheek	0.3 (50) 0.8 (50) 1.5 (75)	6	120	0.5	1.3	51	1.25	10

Table 1. Experimental studies used to calibrate the foot, toe, and cheek skin regions of the 3-D virtual human thermoregulatory model under mild, moderate, and extreme cold-air exposures. Except for *Studies C3* and *C5*, which involved forced convection (wind speed $\geq 0.2 \text{ m}\cdot\text{s}^{-1}$), all other studies involved natural convection (wind speed $< 0.2 \text{ m}\cdot\text{s}^{-1}$). In *Studies C1–C3*, subjects rested in the supine position with bare feet, while in *Studies C4* and *C5*, subjects maintained a sitting posture. Both postures represented an activity intensity of 0.9 MET (metabolic equivalent of task). In *Study C4*, the subjects’ footwear were in direct contact with the cold ground, while *Study C5* did not specify whether such contact occurred and we did not model it. In *Studies C1–C3*, subjects wore only shorts. In *Study C4*, subjects wore a Chinese Army cold-weather uniform, while in *Study C5*, subjects wore a three-layer U.S. Army cold weather clothing system. Simulation of the cold exposure assumed that the experiments commenced at 8:00 a.m. in *Studies C1* and *C2*. For the remaining studies, simulations used the start times as reported in the original articles: 8:00 a.m. in *Study C3*, 10:00 a.m. in *Study C4*, and 8:45 a.m. in *Study C5*. The percentage in parentheses next to the RMSE represents the fraction of predictions that lie within two standard errors of the mean (SEM) of the experimental data. Dashes (-) denote that we did not compute the fraction of predictions that lie within two SEM because the experimental measurement uncertainty was not reported. RMSE: root mean square error.

included mittens (insert, liner, and shell), a microfleece cap and lightweight balaclava, and standard U.S. Army mukluks, which represents a typical clothing ensemble used by U.S. military personnel during cold-weather operations³⁶. We instrumented the subjects with a three-lead electrocardiogram device to monitor heart rate; i-buttons (Thermochron i-button, Model No. DS1921Z-F5, iButtonLink, Whitewater, WI; accuracy $\pm 1.0 \text{ }^{\circ}\text{C}$) to measure index fingertip, dorsum hand, great toe-tip, and dorsum foot skin temperatures; and a calibrated rectal probe (YSI 400 series probe, Measurement Specialties, Hampton, VA, with an accuracy of $\pm 0.1 \text{ }^{\circ}\text{C}$) self-inserted 15 cm beyond the anal sphincter to measure rectal temperature. We also measured oxygen consumption ($\dot{V}_{\text{O}_2}$; TrueOne 2400, Parvo Medics, Salt Lake City, UT) for each subject, which we converted to metabolic equivalent of task (MET) units [$1.0 \text{ MET} = \dot{V}_{\text{O}_2} (\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1})/3.5 (\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1})$], and used it as an input to the model. This study does not meet the definition of a clinical trial. We conducted an observational investigation and did not prospectively assign subjects to any intervention or manipulate their environment to modify health-related biomedical or behavioral outcomes. Instead, we examined their natural physiological responses to cold exposure. The University of Connecticut Institutional Review Board (Storrs, CT) and the U.S. Army Office of Human Research Oversight (Fort Detrick, MD) approved the study protocol, and all methods were performed in accordance with the relevant guidelines and regulations. Each subject provided written informed consent during enrollment into the study.

Model initialization and numerical implementation

In our previous works^{12–14}, we described the procedures for geometry creation, mesh refinement, and mesh and time-step convergence assessment of the model for the average 50th percentile U.S. male. To perform simulations and predict the thermal response throughout the body for a defined set of boundary conditions, we utilized the FE solver COMSOL Multiphysics 5.5 (COMSOL, Inc., Stockholm, Sweden). Briefly, we first determined the initial temperature distribution throughout the body by initializing the model under thermoneutral conditions [i.e., $0.1 \text{ m}\cdot\text{s}^{-1}$ wind speed, $28.0 \text{ }^{\circ}\text{C}$ air temperature, and 40.0% relative humidity, with minimum clothing (shorts; $\sim 0.6 \text{ clo}$) in a resting condition (0.8 MET)], using a two-step process. In the first step, in addition to setting the tissue blood perfusion to basal values, we turned on the passive thermoregulatory mechanisms, including convection, conduction, radiation, and respiration. In the second step, we turned on the active thermoregulatory mechanisms, including vasodilation, vasoconstriction, shivering, sweating, and evaporation, to regulate heat loss, which resulted in an increase in perfusion rate across all tissues. After initializing the virtual human model at the thermoneutral condition, we obtained a T_c of $36.9 \text{ }^{\circ}\text{C}$, $T_{\text{sk,m}}$ of $33.9 \text{ }^{\circ}\text{C}$, average fingertip temperature of $31.1 \text{ }^{\circ}\text{C}$, average toe-tip temperature of $31.8 \text{ }^{\circ}\text{C}$, and cheek skin temperature of $36.1 \text{ }^{\circ}\text{C}$. We then used these values as the starting point to simulate the experimental conditions in each of the studies in Table 2 (*Studies V1–V8*). In these simulations, we turned off the CIVD component of the model because this mechanism is only present in a subset of individuals and exhibits substantial between-individual variability due to different factors,

Study	Measurement Site	RMSE, °C (Fraction, %)	No. of Subjects	Duration (min)	Exposure Temp. (°C)	Wind Speed (m·s ⁻¹)	Relative Humidity (%)	Clothing (clo)	Source
V1	Rectum Dorsum hand Dorsum foot Face	0.1 (100) 1.5 (100) 1.2 (100) 2.6 (100)	6	60	−40.0	0.4	50	3.08	28
V2	Rectum Ring fingertip Great toe-tip	0.2 (39) 2.7 (74) 3.4 (50)	8	180	−25.0	0.6	40	3.60	29
V3	Gastrointestinal tract Middle fingertip Cheek	0.1 (100) 2.2 (70) 2.1 (56)	12	105	−20.0	0.1	65	2.16	30
V4	Rectum Whole-body mean Middle fingertip Great toe-tip	0.1 (100) 1.8 (3) 1.6 (59) 3.5 (50)	6	160	−15.0	0.6	40	2.60	31
V5	Rectum Whole-body mean Dorsum foot Cheek	0.1 (100) 0.6 (25) 0.2 (100) 2.7 (0)	10	60	−15.0	3.0	40	3.60	32
V6	Rectum Dorsum hand Dorsum foot Index fingertip Great toe-tip	0.1 (100) 1.3 (96) 1.0 (100) 1.9 (83) 1.2 (96)	15	120	−10.0	1.0	40	3.60	†
V7	Rectum Whole-body mean	0.5 (31) 1.6 (25)	9	120	1.0	0.8	40	0.57	17
V8	Rectum Whole-body mean	0.1 (100) 0.5 (58)	9	60	12.0	0.1	45	0.57	19

Table 2. Experimental studies used to validate the 3-D virtual human thermoregulatory model under mild, moderate, and extreme cold-air exposures. In all studies, core body temperature was measured with a rectal probe, except for *Study V3*, where it was measured using ingestible temperature capsules. Except for *Studies V3* and *V8*, which involved natural convection (wind speed $< 0.2 \text{ m}\cdot\text{s}^{-1}$), all other studies involved forced convection (wind speed $\geq 0.2 \text{ m}\cdot\text{s}^{-1}$). In *Studies V1–V4*, *V6*, and *V8*, subjects maintained a sitting posture; in *Study V5*, subjects maintained a standing posture; and in *Study V7*, subjects rested in the supine position. All postures represented an activity intensity of 0.9 MET (metabolic equivalent of task). In *Studies V3*, *V5*, and *V6*, the subjects' footwear were in direct contact with the cold ground, while the remaining studies did not specify whether such contact occurred and we did not model it. Clothing ensembles varied across studies. In *Study V1*, subjects wore the typical military extreme-cold protective clothing ensemble used by the U.S. Army, the Canadian Department of National Defence, and the Norwegian military. In *Studies V2* and *V4*, subjects wore the Canadian Forces Arctic Clothing Ensemble, with three or two layers, respectively; in *Study V3*, subjects wore a Chinese Army cold-weather uniform; in *Studies V5* and *V6*, subjects wore the U.S. Army Cold-weather Clothing System; while in *Studies V7* and *V8*, subjects wore only shorts. Simulation of the cold exposure used the start times reported in the original articles: 12:00 p.m. in *Study V1* and 10:00 a.m. in *Studies V2* and *V3*. Simulations for *Studies V4–V8* assumed that the experiments commenced at 8:00 a.m. For *Study V3*, we calculated the root mean square error (RMSE) across all three phases of the study—pre-conditioning, cold exposure, and rewarming. In contrast, for the remaining studies, we calculated the RMSE solely for the cold-exposure phase. The percentage in parentheses next to the RMSE represents the fraction of predictions that lie within two standard errors of the mean of the experimental data. †Study conducted in an environmentally controlled chamber at the University of Connecticut (see text).

including differences in surface area to volume ratio in the fingers and toes^{37,38}. Therefore, by turning off CIVID, we ensured consistency between experimental measurements and model predictions, each of which describes group-average results.

In the model, we incorporated temperature-dependent nonlinear material properties, which resulted in a nonsymmetric Jacobian matrix that required significant memory to solve the set of coupled nonlinear partial differential equations. We used the *nojac* operator within the COMSOL software to optimize memory usage and solution time, as well as to improve the convergence of the nonlinear solver. We performed all simulations using a 2.60-GHz 16-core Intel Xeon Gold workstation with 128-GB RAM and two processors, which required 27 to 174 h of central processing unit (CPU) time to perform the simulations in Table 2, which ranged from 60 to 180 min. We refer the reader to our previous works^{12,14} for additional information on the numerical implementation.

To assess the accuracy of the model-predicted core body temperature and skin temperatures, we computed 1) the RMSE between the predicted and measured values and 2) the fraction of model predictions that lie within two standard errors of the experimental mean (SEM), which represents the range where 95% of the mean values of a future experiment are expected to lie. Taken together, these two complementary metrics quantify both the magnitude of the prediction error and the extent to which the predictions fall within the expected variability

of the experimental data, thereby offering an informative assessment of model performance. Because the initial measurements of core body temperature and skin temperature varied between studies and did not always exactly match the model-predicted values at time zero, we reported all temperatures as changes relative to their initial, time-zero values measured in the studies or predicted by the model.

Results
Model calibration

We calibrated the extended 3-D model by identifying convective heat-transfer coefficients for the dorsum foot, toe-tip, and cheek skin regions using the experimental data in *Studies C1-C5* in Table 1. For each of these two body regions (foot/toe-tip and cheek), we separately calibrated the coefficients for natural convection and forced convection cold-air exposures under barefoot or bare-face conditions, respectively, until the model-predicted skin temperatures matched the experimental values, resulting in RMSEs of ≤ 2.3 °C. For forced convection¹², we calibrated the heat-transfer coefficient C and exponent e in Eq. (3) one at a time, where we first fixed e and updated C, and then fixed C to its final value and updated e. Similarly, we used the same methodology to determine the natural convection coefficient N. Based on the work of Hertzman and Randall³⁹, we also reduced the baseline blood perfusion rate $\dot{\omega}_{b,0}$ for the foot and toe-tip regions from 7.00×10^{-4} to 5.04×10^{-4} m³·s⁻¹·m⁻³ to better match the experimental data. Table 3 shows the values of the calibrated heat-transfer coefficients and their corresponding sources. The calibrated model accurately traced the changes in skin temperature for the dorsum foot and toe-tip with RMSEs ≤ 0.8 °C (Supplementary Figure S2) as well as for the cheek, albeit with larger RMSEs ranging from 1.5 to 2.3 °C (Supplementary Figure S3). Supplementary Figures S4 and S5 show the model-predicted temperature changes at the rectum (core body) ΔT_c and at the skin of the whole body $\Delta T_{sk,m}$ with average RMSEs of 0.2 °C and 1.1 °C, respectively.

Model validation

Using the eight distinct studies in Table 2, we validated the model by comparing model-predicted ΔT_c and changes in skin temperatures (mean whole body, dorsum hand, fingertip, cheek, dorsum foot, and toe-tip) with the corresponding experimental data reported in the studies for mild to extreme cold air, with ambient air temperature ranging from -40.0 to 12.0 °C, wind speed from 0.1 to 3.0 m·s⁻¹, clothing insulation from 0.6 to 3.6 clo, and study duration from 60 to 180 min. In these studies, the subjects either maintained a sitting posture, rested in the supine position, or maintained a standing posture, with all postures representing an activity intensity of 0.9 MET. While all studies reported core body temperature, measurements at other body regions varied from study to study. In addition, for the reasons discussed in Materials and Methods, in these simulations we turned off the CIVD component of the model¹⁴.

Core body temperature

Figures 1A, 2A, 3A, 4A, 5A, 6A, 7A and 8A show the comparison between the model-predicted changes in core body temperature ΔT_c at the rectum (solid black line) and the experimental data (solid black circles) across the eight studies in Table 2, which yielded an average RMSE of 0.2 °C with the predictions invariably falling within two SEM of the experimental data. The only exception was for data points in *Studies V2* and *V7*, where the fraction of predictions that fell within two SEM of the measurements ranged between 31 and 39%. For *Study V2*, the model predictions matched the experimental data well up to 90 min, with a maximum difference of 0.2 °C. However, after 90 min, the model overpredicted the decrease in T_c , with a difference of 0.3 °C between the experimental data and the model prediction at the end of the cold-exposure period, likely due to an increase in metabolic rate (non-shivering thermogenesis). For *Study V7*, while the experimental data showed very small changes from the initial value, the model also overpredicted the decrease in T_c , with a difference in temperature of 0.8 °C at 120 min. This discrepancy likely reflected an increased body heat loss to the environment predicted by the model, which exceeded the model-generated heat due to shivering under the experimental condition. This was the only study where the model-predicted trends did not adequately match the experimental data. Nevertheless, given the range of combinations of the experimental conditions, which resulted in different trends in the measured ΔT_c , these results indicated that the model predictions accurately captured changes in core body temperature.

The experimental data revealed one of three general trends: a stable ΔT_c with changes < 0.1 °C throughout the duration of the experiment, as observed in *Study V1* (Fig. 1A); a nearly monotonic decrease in ΔT_c by as much as < 0.6 °C after the onset of cold exposure, as observed in *Studies V2, V4, and V8* (Figs. 2A, 4A, and 8A, respectively); or an initial rise in ΔT_c followed by a gradual decline to as much as 0.3 °C, as observed in *Studies V3, V5, V6, and V7* (Figs. 3A, 5A, 6A, and 7A, respectively).

By and large, the model predictions followed the general trend in the measured ΔT_c , with a tendency to produce a slight initial increase in ΔT_c followed by a gradual decrease, as observed in seven of the eight predictions (*Studies V1-V4, V6-V8*). This initial rise in ΔT_c can be attributed to three factors: (1) a rapid decrease in skin

Body Segment	Natural Convection Coefficient ^a [N]	Forced Convection Coefficient [C]	Forced Convection Exponent [e]	Source
Dorsum foot/toe-tip	3.11 ^{a-c}	13.40 ^a	0.56 ^a	[a8, [b22[c62]
Cheek	2.52 ^{a, b}	5.20 ^a	0.50 ^a	[a8, [b22

Table 3. Calibrated heat-transfer coefficients for the foot and cheek skin regions. Natural convection: wind speed < 0.2 m·s⁻¹; forced convection: wind speed ≥ 0.2 m·s⁻¹.

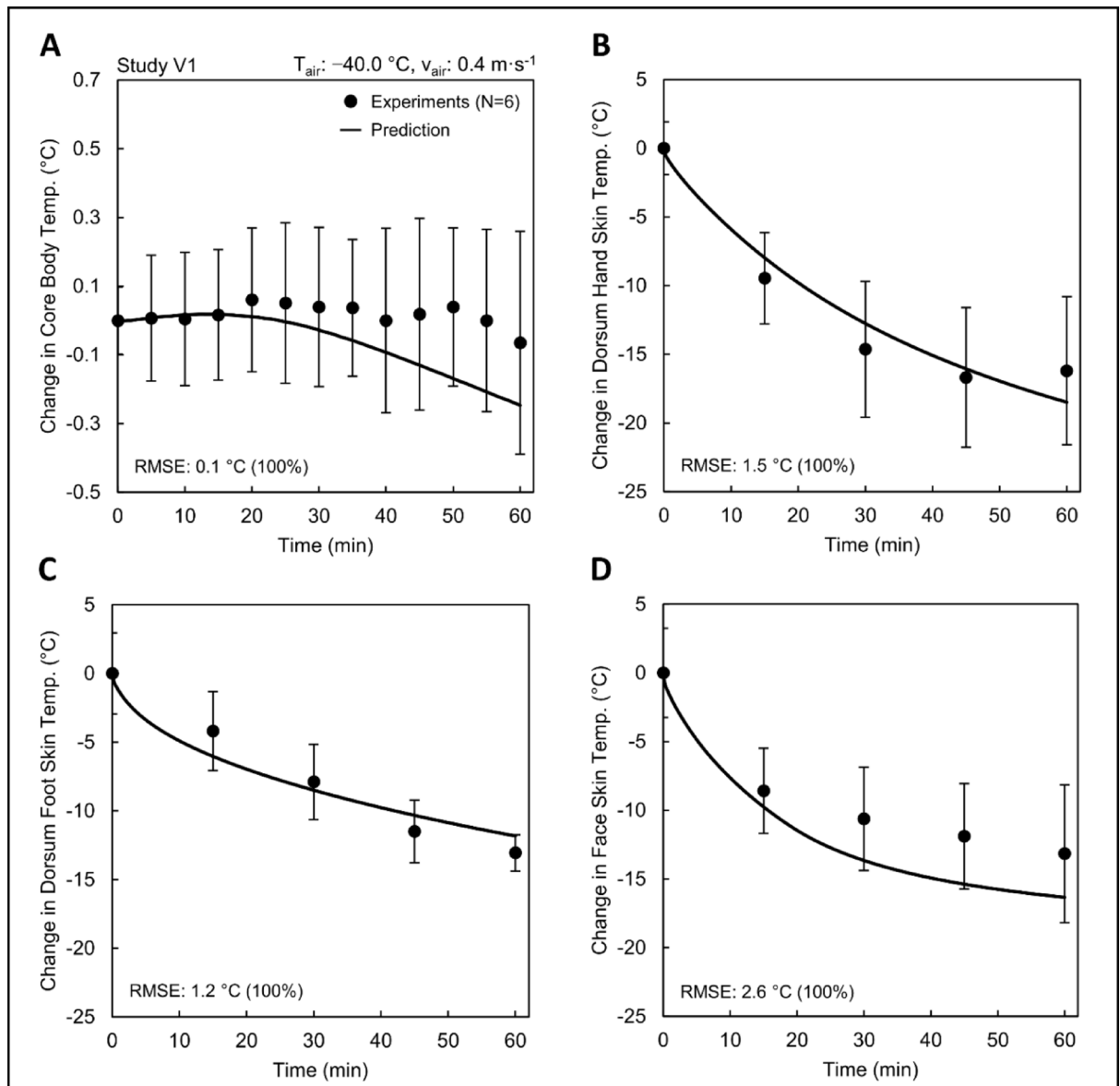


Fig. 1. Model validation of (A) core body temperature at a depth of 15 cm beyond the anal sphincter, (B) dorsum hand skin temperature (average of the fingertip and thumb-tip), (C) dorsum foot skin temperature, and (D) face skin temperature (average of the ear lobes and nose) for *Study V1* (Table 2), in which six subjects wearing an Arctic clothing ensemble (3.08 clo) sat in a cold chamber [air temperature (T_{air}): $-40.0\text{ }^{\circ}\text{C}$; wind speed (v_{air}): $0.4\text{ m}\cdot\text{s}^{-1}$] for 60 min. The clothing ensemble included a thermal undershirt, long johns, and a fleece jacket as well as bib pants plus a winter parka, balaclava, Hy-Arctic Shell mittens, and cold-wet boots. In each panel, the solid black circles denote the average of the experimentally measured temperature change, the vertical black bars indicate two standard errors of the mean (SEM), the solid black line denotes the model-predicted temperature, and the percentages in parentheses next to the root mean square error (RMSE) represent the fraction of predictions that lie within two SEM. N: number of subjects.

blood flow caused by cutaneous vasoconstriction, which limited the delivery of warm blood from the core to the skin; (2) an initial increase in heat generation due to shivering; and (3) heat recovery by the venous blood returning to the body core through partial heat exchange with tissue at the capillary level and countercurrent heat exchange with major arteries. Specifically, as warm blood passed down the arteries, it gave up some of its heat to the colder blood returning from the extremities in the veins, allowing the body to recover heat. Subsequently, the rate of heat dissipation from the skin to the surrounding environment exceeded the rate of heat generation at the core, resulting in a decrease in the temperature of the venous blood returning to the core, and ultimately causing a decrease in ΔT_c . Most notably, in *Study V3*, which involved a rewarming phase after a $-20.0\text{ }^{\circ}\text{C}$ cold-air exposure for 30 min, the model predictions followed the experimental data closely for the entire duration of the experiment and successfully captured the “after-drop” phenomenon during rewarming (times between 65 and 105 min in Fig. 3A), wherein the ΔT_c continued to drop for ~ 25 min into the rewarming phase. In contrast, for

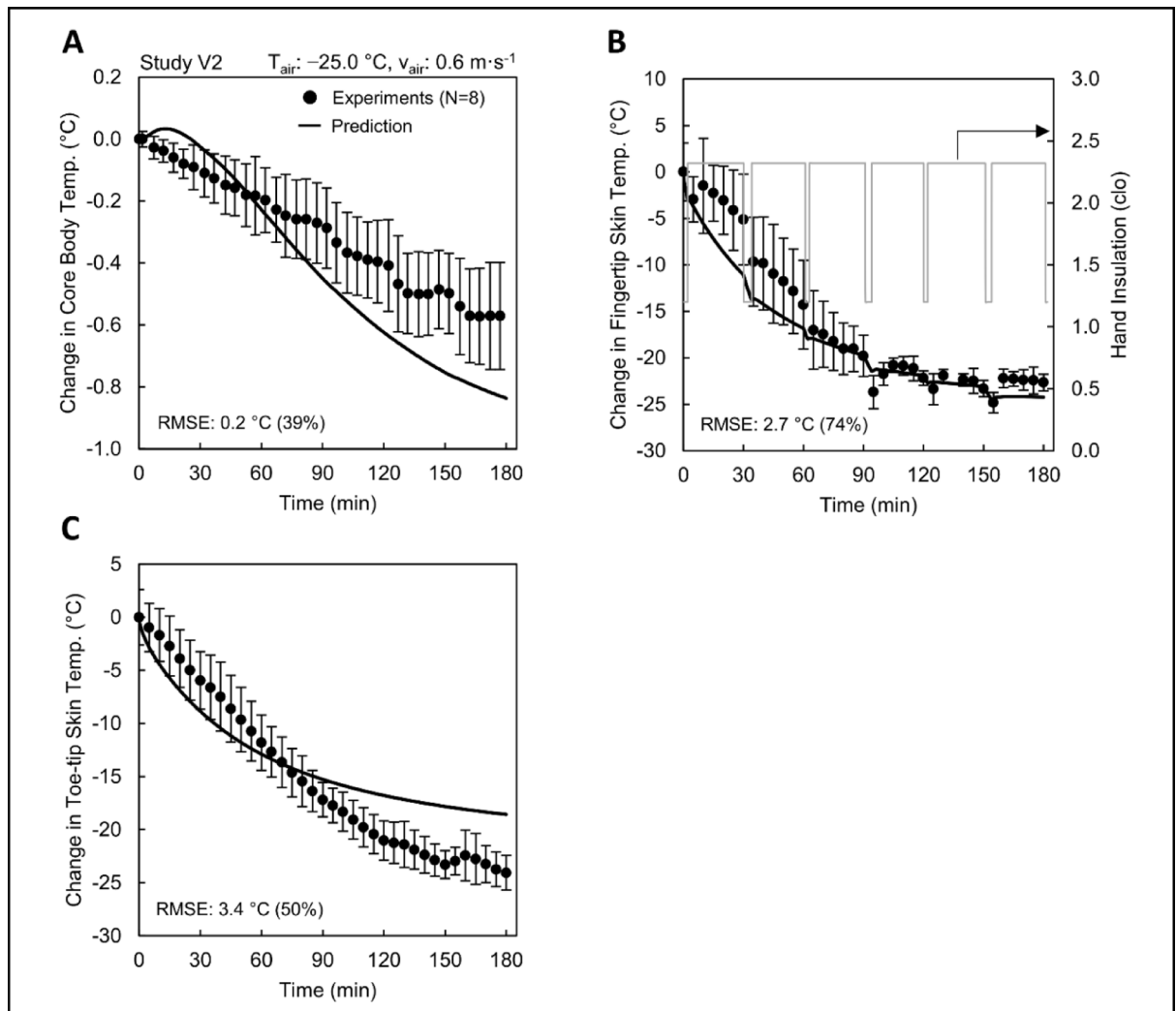


Fig. 2. Model validation of (A) core body temperature at a depth of 15 cm beyond the anal sphincter, (B) ring fingertip skin temperature (fourth finger from the thumb side), and (C) great toe-tip skin temperature for *Study V2* (Table 2), in which eight subjects wearing a three-layer Arctic clothing ensemble (3.60 clo) sat in a cold chamber [air temperature (T_{air}): $-25.0\text{ }^{\circ}\text{C}$; wind speed (v_{air}): $0.6\text{ m}\cdot\text{s}^{-1}$] for 180 min. Prior to the cold exposure, subjects sat outside of the cold chamber for at least 45 min at an ambient temperature of $25.0\text{ }^{\circ}\text{C}$ and became familiar with the dexterity tasks, while wearing the same Arctic clothing to cover their upper body region and only shorts on their lower body region. The three-layer clothing system included a fleece garment, an uninsulated inner parka and pants, and an insulated outer parka and pants. Subjects also wore a thin pair of long, cotton underwear under the fleece pants and a standard Canadian Force mukluk, woolen socks, and a lightweight balaclava. Note that the 3.60-clo Arctic clothing ensemble reported in the original article did not consider the long, cotton underwear worn under the fleece pants (a clo value of 0.30), which was accounted for while allocating local thermal resistance at the leg skin region. During the cold exposure, subjects performed a dexterity task using either the Purdue Pegboard test (PP test) or a C-7 rifle assembly and disassembly task every 30 min, during which time two out of three layers of the gloves were removed, resulting in a reduction in hand insulation. Subjects completed the C-7 rifle task at 0, 60, 120, and 180 min for ~ 2 min, whereas they completed the PP test at 30, 90, and 150 min for ~ 4 min. In each panel, the solid black circles denote the average of the experimentally measured temperature change, the vertical black bars indicate two standard errors of the mean (SEM), the solid black line denotes the model-predicted temperature, and the percentages in parentheses next to the root mean square error (RMSE) represent the fraction of predictions that lie within two SEM. The solid gray line in panel B indicates the hand insulation as shown on the secondary y-axis. N: number of subjects.

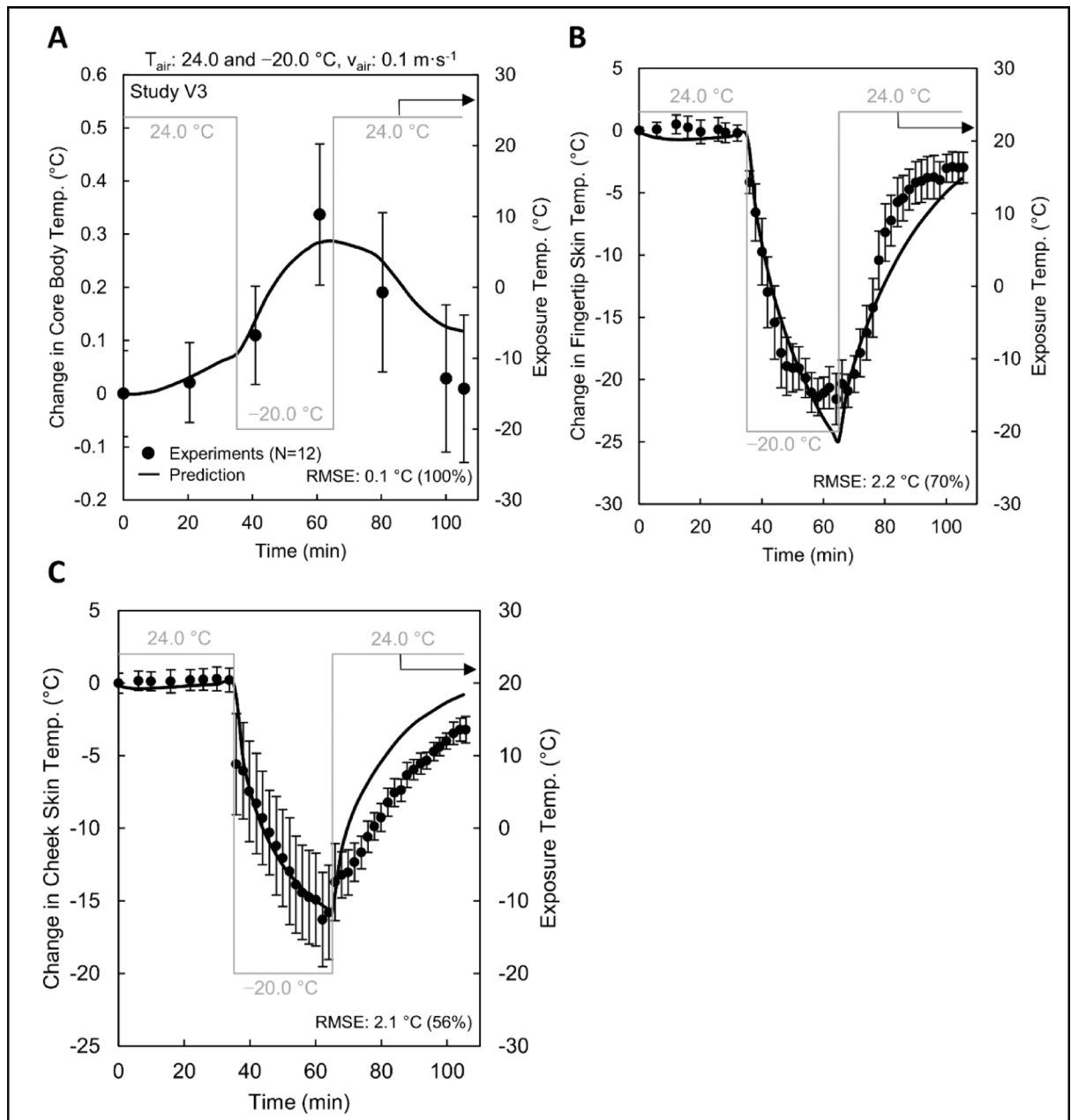


Fig. 3. Model validation of (A) core body temperature measured in the gastrointestinal tract using an ingestible temperature capsule, (B) middle fingertip skin temperature, and (C) cheek skin temperature for Study V3 (Table 2), in which 12 subjects wore a Chinese Army cold-weather uniform (2.16 clo) while sitting for 105 min in still air to complete a three-phase experiment: 1) an adaptation or pre-conditioning phase of 35 min at an air temperature (T_{air}) of 24.0 °C, 2) an extreme cold-air exposure phase of 30 min at T_{air} -20.0 °C, and 3) a rewarming phase of at least 40 min at T_{air} 24.0 °C. During all three phases, the subjects' footwear were in direct contact with the cold ground. We used a temperature profile at the bottom of the footwear so as to consider the conductive heat loss resulting from the contact between the shoe sole and the ground. The cold-protective clothing included a long-sleeve coat, trousers, a cotton coat, cotton pants, cotton socks, boots, and a hat. In each panel, the solid black circles denote the average of the experimentally measured temperature change, the vertical black bars indicate two standard errors of the mean (SEM), the solid gray line indicates T_{air} , the solid black line denotes the model-predicted temperature, and the percentages in parentheses next to the root mean square error (RMSE) represent the fraction of predictions that lie within two SEM. N: number of subjects; v_{air} : wind speed.

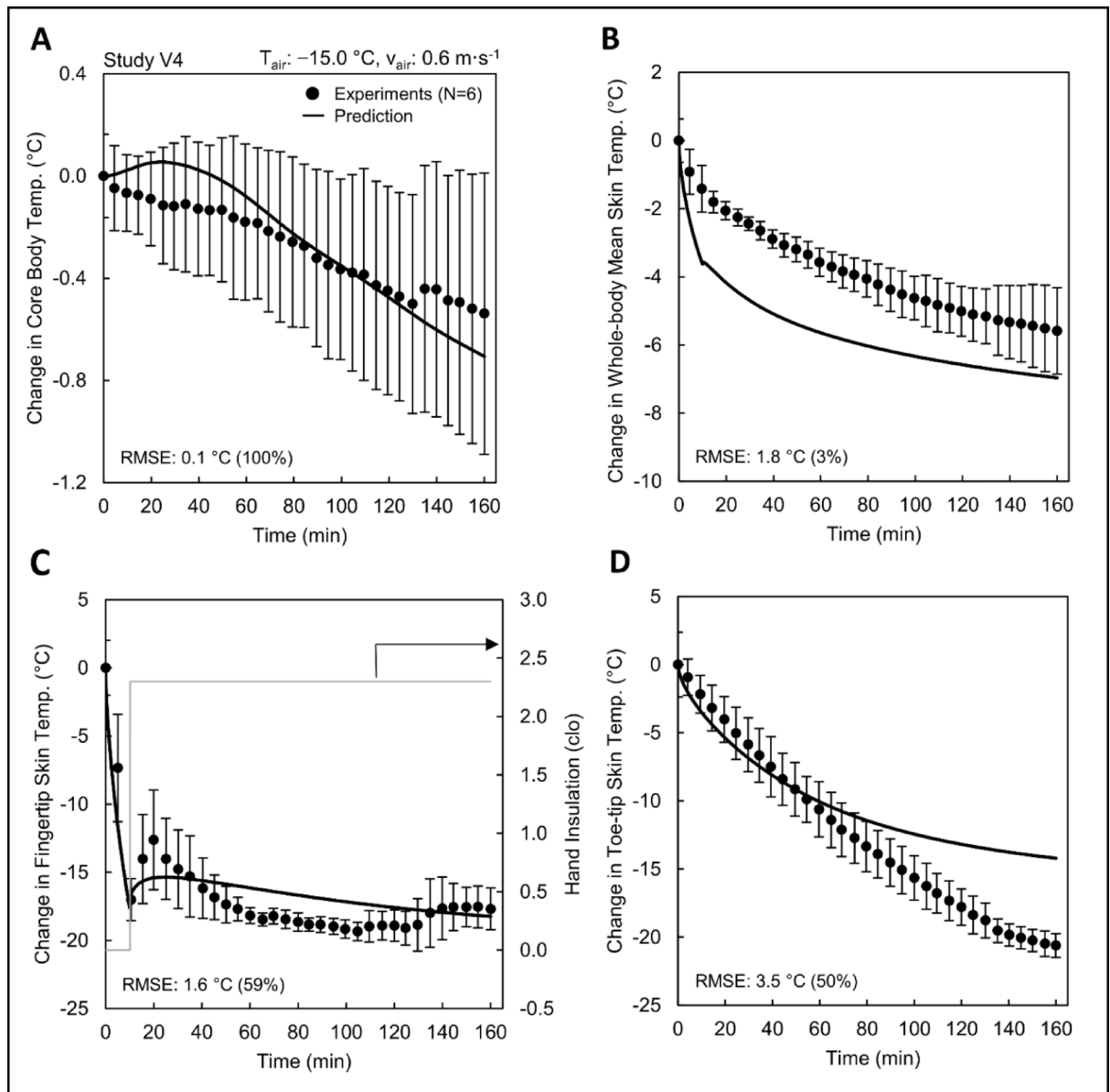


Fig. 4. Model validation of (A) core body temperature at a depth of 15 cm beyond the anal sphincter, (B) whole-body mean skin temperature, (C) middle fingertip skin temperature, and (D) great toe-tip skin temperature for *Study V4* (Table 2), in which six subjects wearing a two-layer Canadian Forces (CF) Arctic clothing ensemble (2.60 clo) sat bare handed for the first 10 min and then with Arctic mittens for the remaining 150-minute exposure in a cold chamber [air temperature (T_{air}): -15.0°C ; wind speed (v_{air}): $0.6\text{ m}\cdot\text{s}^{-1}$]. (One subject dropped out of the study at $\sim 135\text{ min}$.) The Arctic clothing ensemble included a fleece garment (jacket and pants), uninsulated jacket and pants, a thin pair of long, cotton underwear worn under the fleece pants, and a standard CF mukluk, woolen socks, and a lightweight balaclava. In each panel, the solid black circles denote the average of the experimentally measured temperature change, the vertical black bars indicate two standard errors of the mean (SEM), the solid black line denotes the model-predicted temperature, and the percentages in parentheses next to the root mean square error (RMSE) represent the fraction of predictions that lie within two SEM. The solid gray line in panel C indicates the hand insulation as shown on the secondary y-axis. N: number of subjects.

Study V5 (Fig. 5A), where subjects maintained a standing posture for 60 min at -15.0°C , the model predicted no change in ΔT_c and closely tracked the experimental measurements throughout the trial. This trend likely reflects a thermal balance between heat generation due to shivering and heat dissipation from the surface of the body.

Whole-body mean skin temperature

We compared the model-predicted changes in whole-body mean skin temperature $\Delta T_{\text{sk,m}}$ with the experimental data for the four studies that reported $T_{\text{sk,m}}$ (*Studies V4, V5, V7, and V8*). *Studies V4* and *V5* involved extreme-

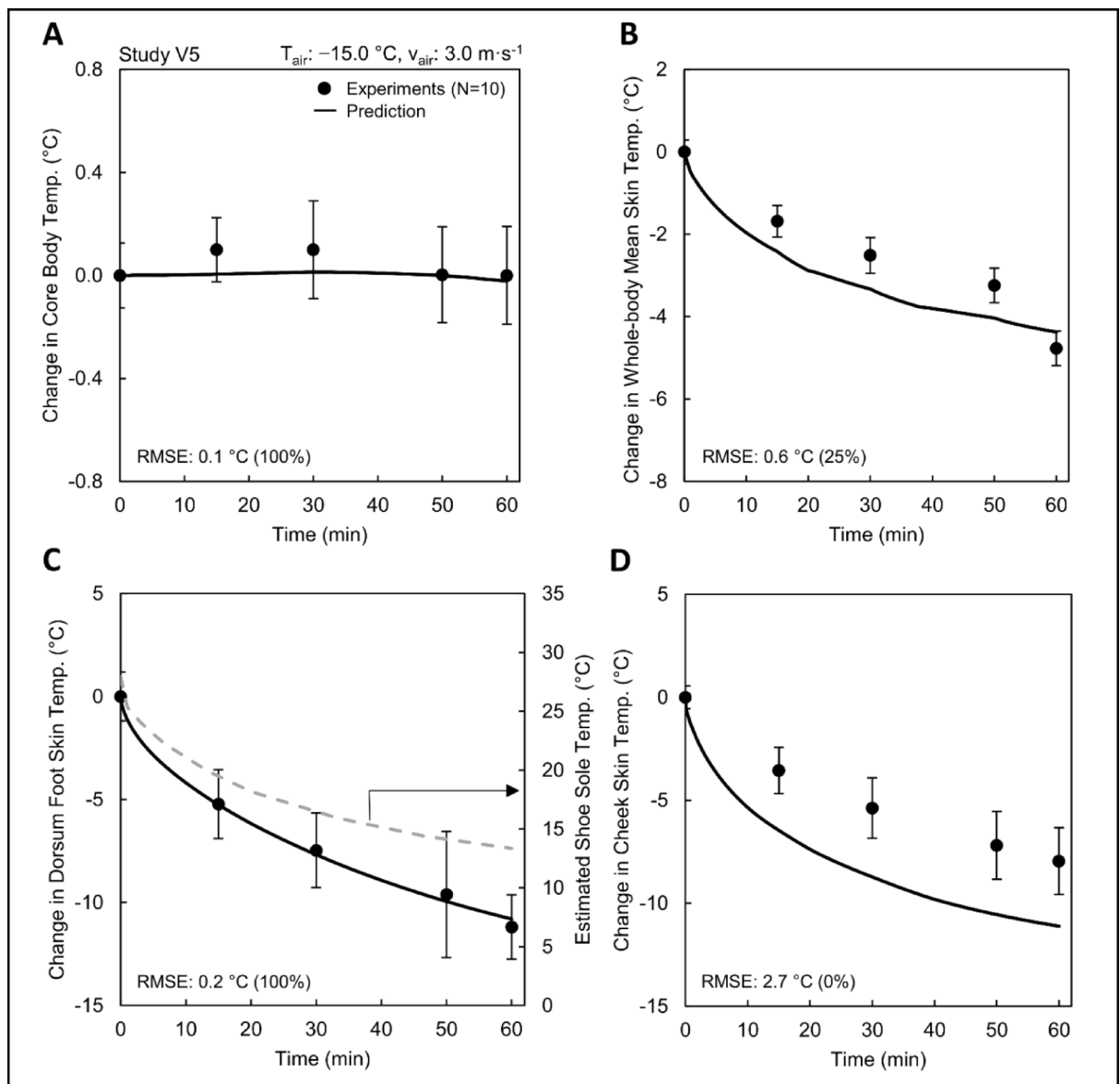


Fig. 5. Model validation of (A) core body temperature at a depth of 10 cm beyond the anal sphincter, (B) whole-body mean skin temperature, (C) dorsum foot skin temperature, and (D) cheek skin temperature for Study V5 (Table 2), in which 10 subjects wearing a three-layer U.S. Army Extended Cold-weather Clothing System (3.60 clo) stood in a cold chamber [air temperature (T_{air}): $-15.0\text{ }^{\circ}\text{C}$; wind speed (v_{air}): $3.0\text{ m}\cdot\text{s}^{-1}$] for 60 min, while covering their head with a microfleece cap, face with a balaclava, hands with Arctic mittens, and feet with cold-wet boots. For the duration of the exposure, the subjects' footwear were in direct contact with the cold ground. We used a temperature profile at the bottom of the footwear so as to consider the conductive heat loss resulting from the contact between the shoe sole and the ground. In each panel, the solid black circles denote the average of the experimentally measured temperature change, the vertical black bars indicate two standard errors of the mean (SEM), the solid black line denotes the model-predicted temperature, and the percentages in parentheses next to the root mean square error (RMSE) represent the fraction of predictions that lie within two SEM. The dashed gray line in panel C indicates the shoe sole temperature profile as shown on the secondary y-axis. N: number of subjects.

cold conditions, with both experiments conducted at an air temperature of $-15.0\text{ }^{\circ}\text{C}$, while Studies V7 and V8 focused on moderate ($1.0\text{ }^{\circ}\text{C}$) and mild ($12.0\text{ }^{\circ}\text{C}$) cold-air exposures, respectively (Table 2). Overall, our simulations adequately captured the temporal dynamics of the experimental measurements over the entire duration of each experiment, with RMSEs ranging from 0.5 to $1.8\text{ }^{\circ}\text{C}$. As shown in Figs. 4B, 5B and 7B, and 8B, the predicted $\Delta T_{\text{sk,m}}$ dropped upon exposure to the cold environment across all four studies, primarily due to vasoconstriction and significant convective and radiative heat loss to the ambient air, followed by a more gradual decline. We observed a discrepancy in our predictions for Study V4 (Fig. 4B), with only 3% of the predictions falling within two SEM of the measurements. In Study V4, the model predicted a much faster initial drop in

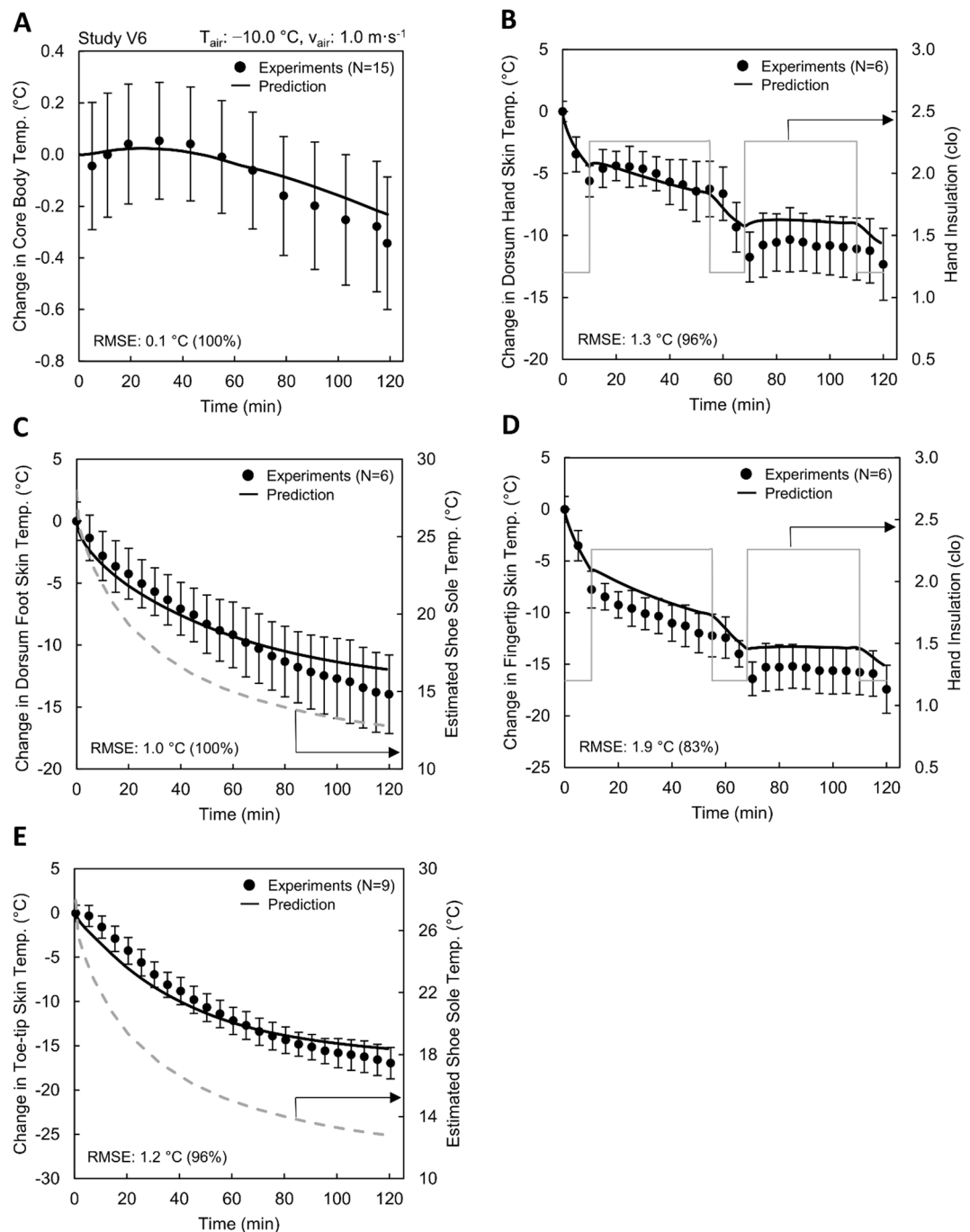


Fig. 6. Model validation of (A) core body temperature at a depth of 15 cm beyond the anal sphincter ($N=15$ subjects), (B) dorsum hand skin temperature ($N=6$), (C) dorsum foot skin temperature ($N=6$), (D) index fingertip skin temperature ($N=6$), and (E) great toe-tip skin temperature ($N=9$) for *Study V6* (Table 2), in which subjects wearing a three-layer U.S. Army Extended Cold-weather Clothing System (3.60 clo) sat in a cold chamber [air temperature (T_{air}): -10.0 °C; wind speed (v_{air}): 1.0 m·s $^{-1}$] for 120 min, while covering their head with a microfleece cap, face with a lightweight balaclava, hands with Arctic mittens (insert, liner, and shell), and feet with standard U.S. Army mukluks. During the cold exposure, subjects also performed a dexterity task using the Purdue Pegboard test after the first 10 min and then every 40 min for 10 min, during which time two out of three layers of the gloves were removed, resulting in a reduction in hand insulation. For the duration of the exposure, the subjects' footwear were in direct contact with the cold ground. We used a temperature profile at the bottom of the footwear so as to consider the conductive heat loss resulting from the contact between the shoe sole and the ground. In each panel, the solid black circles denote the average of the experimentally measured temperature change, the vertical black bars indicate two standard errors of the mean (SEM), the solid black line denotes the temperature predictions from the virtual human model, and the percentages in parentheses next to the root mean square error (RMSE) represent the fraction of predictions that lie within two SEM. The solid gray line in panels B and D indicates the hand insulation, and the dashed gray line in panels C and E indicates the shoe sole temperature profile as shown on the secondary y-axis.

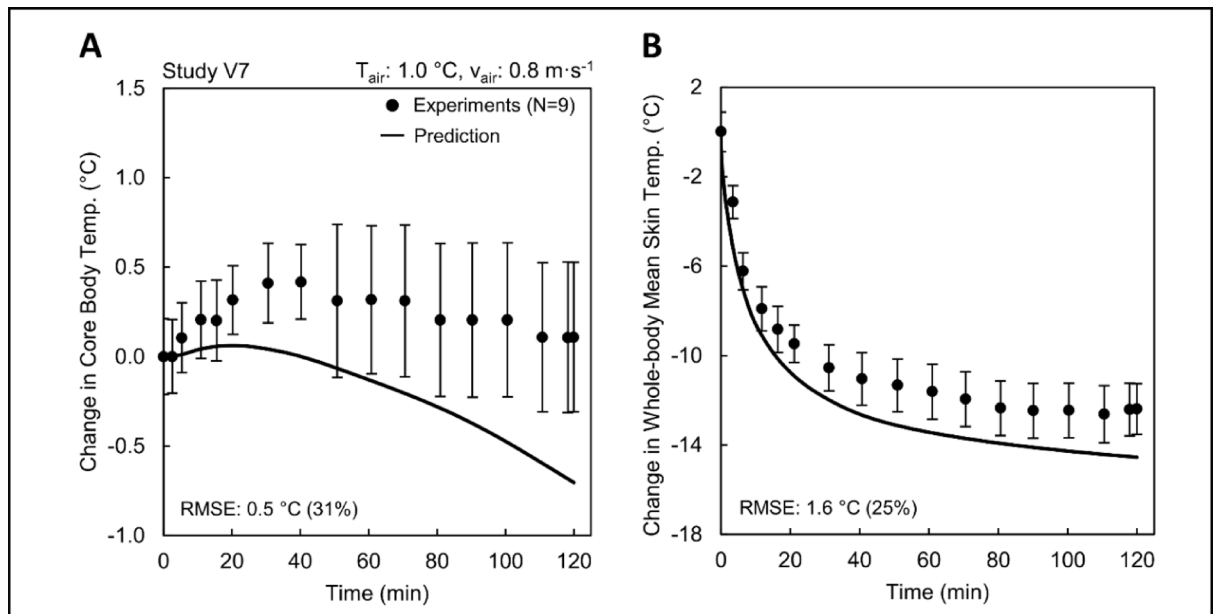


Fig. 7. Model validation of (A) core body temperature at a depth of 12 cm beyond the anal sphincter and (B) whole-body mean skin temperature for *Study V7* (Table 2), in which nine subjects wearing only jogging shorts or a bathing suit (0.57 clo) sat in a cold chamber [air temperature (T_{air}): 1.0 °C; wind speed (v_{air}): 0.8 m·s⁻¹] for 120 min. In each panel, the solid black circles denote the average of the experimentally measured temperature change, the vertical black bars indicate two standard errors of the mean (SEM), the solid black line denotes the model-predicted temperature, and the percentages in parentheses next to the root mean square error (RMSE) represent the fraction of predictions that lie within two SEM. N: number of subjects.

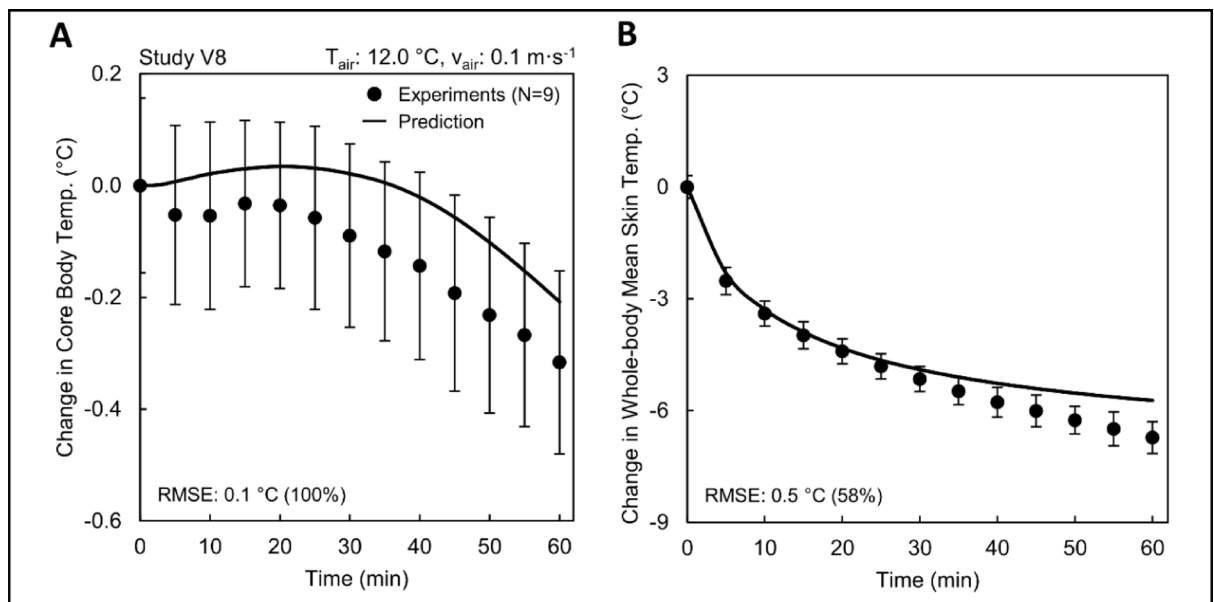


Fig. 8. Model validation of (A) core body temperature at a depth of 10 cm beyond the anal sphincter and (B) whole-body mean skin temperature for *Study V8* (Table 2), in which nine subjects wearing only swimming trunks (0.57 clo) sat in a cold chamber [air temperature (T_{air}): 12.0 °C; wind speed (v_{air}): 0.1 m·s⁻¹] for 60 min. In each panel, the solid black circles denote the average of the experimentally measured temperature changes, the vertical black bars indicate two standard errors of the mean (SEM), the solid black line denotes the model-predicted temperature, and the percentages in parentheses next to the root mean square error (RMSE) represent the fraction of predictions that lie within two SEM. N: number of subjects.

$\Delta T_{sk,m}$, with a cooling rate of 0.4 °C/minute for the first 10 min, compared to the experimental observations, which yielded a rate of 0.1 °C/minute. This discrepancy is likely due to the warmer initial $T_{sk,m}$ value at time zero in the simulations as compared to the experimental data (34.0 °C versus 32.5 °C), which resulted in a larger gradient with the air temperature and a faster drop in skin temperature. Following this initial discrepancy, the model predictions better matched the gentle decrease in $T_{sk,m}$ that persisted for the remainder of the cold exposure, where shivering increased steadily in our model predictions followed by a continual decline in core body temperature (Fig. 4A). For *Studies* V5, V7, and V8, the fraction of predictions that fell within two SEM of the measurements ranged from 25 to 58%, with differences in temperature between the experimental data and the model predictions at the end of the cold-exposure period of 0.4 °C for *Study* V5 (Fig. 5B), 2.2 °C for *Study* V7 (Fig. 7B), and 1.0 °C for *Study* V8 (Fig. 8B).

Dorsum hand and fingertip skin temperature

We compared the model-predicted changes in dorsum hand and fingertip skin temperatures with the experimental data for the five studies that reported these values (*Studies* V1–V4 and V6), with air temperature ranging from –40.0 to –10.0 °C and exposure durations of 60 to 180 min. Overall, the model predictions closely followed the trends in the experimental data across all five studies, with RMSEs ranging from 1.3 to 2.7 °C and fraction of predictions within two SEM ranging from 59 to 100%, while capturing the temperature fluctuations influenced by both hand insulation and exposure temperature.

Figure 1B shows that the model predictions adequately captured the quick drop in dorsum hand skin temperature in *Study* V1, closely tracking the trend in the experimental data throughout the entire experiment, yielding a RMSE of 1.5 °C and all predictions falling within two SEM of the experimental data. Similarly, Fig. 6B demonstrates that the model effectively reproduced the changes in dorsum hand skin temperature in *Study* V6, yielding a RMSE of 1.3 °C and 96% of the predictions falling within two SEM of the measurements. The model predicted the fingertip skin temperature for *Studies* V2–V4 and V6 reasonably well, matching the measured data across the entire duration of the experiments, with RMSEs ranging from 1.6 to 2.7 °C and fraction of predictions within two SEM ranging from 59 to 83% (Figs. 2B, 3B and 4C, and 6D, respectively). The results also indicate that the model captured changes in fingertip skin temperature resulting from variations in hand insulation during the cold-air exposure in *Studies* V2 and V6, where subjects intermittently removed their gloves to perform hand-dexterity tasks, as well as the dynamic temperature changes across all three phases of *Study* V3 (Fig. 3B): a 35-minute pre-conditioning phase at an air temperature of 24.0 °C, a 30-minute extreme cold-air exposure phase at –20.0 °C, and a recovery phase of 40 min at 24.0 °C, yielding an overall RMSE of 2.2 °C. The model also captured the dynamics in *Study* V4 (Fig. 4C), where subjects were barehanded during the initial 10 min of cold exposure, before putting on Arctic mittens and wearing them for the remainder of the experiment. By and large, the model adequately predicted the initial drop in fingertip skin temperature when the hand was bare for 10 min, with a difference of 0.6 °C between the experimental data and the model-predicted value. In addition, the model partially captured the subsequent rise in fingertip temperature due to hand insulation, followed by a gradual drop, with a difference of 0.6 °C at the end of the exposure.

Dorsum foot and toe-tip skin temperature

We compared the model-predicted changes in dorsum foot and toe-tip skin temperatures with experimental data across five studies (*Studies* V1, V2, and V4–V6) conducted at air temperatures ranging from –40.0 to –10.0 °C and exposure durations of 60 to 180 min. Overall, the model predictions followed the experimental trends across all five studies, with RMSEs ranging from 0.2 to 3.5 °C and fraction of predictions within two SEM ranging from 50 to 100%.

In *Studies* V5 and V6, the subjects' footwear were in direct contact with the cold ground, while the remaining studies did not specify whether such contact occurred. In *Studies* V1, V5, and V6 (Figs. 1C and 5C, and 6C, respectively), the model predictions for the dorsum foot skin temperature captured the temporal evolution observed in the experimental data, with RMSEs ranging from 0.2 to 1.2 °C and all predictions falling within two SEM of the measurements.

In *Study* V6 involving direct footwear (U.S. Army mukluks) contact with the cold ground, the model accurately reflected the experimental trends for toe-tip skin temperatures (Fig. 6E), yielding a RMSE of 1.2 °C and with 96% of the predictions falling within two SEM of the measurements. In contrast, for *Studies* V2 and V4, the model underpredicted the decrease in toe-tip skin temperature at the end of the exposure with large RMSEs of 3.4 and 3.5 °C, respectively, and only 50% of the predictions falling within two SEM of the measurements (Figs. 2C and 4D, respectively). In particular, the differences between the experimental data and the model predictions at the end of the cold-exposure period were 5.5 °C for *Study* V2 and 6.4 °C for *Study* V4. Most notably, for *Studies* V2 and V4, the experimentally measured toe-tip skin temperatures exhibited a nearly monotonic linear decreasing trend, whereas the model-predicted skin temperatures decreased in an exponential-like manner. Accordingly, the model overpredicted the decrease in temperature in the early- to mid-phases of the study and underpredicted the decrease in the final phase. This discrepancy likely stems from uncertainties related to the thermal insulation properties of the cold-weather footwear (mukluks). Mukluks are a type of cold-weather boots that feature a thick rubber outsole, an insulated insole, and a weather-resistant cotton or wool interior, often rated with insulation values of 2.0 clo or higher^{40,41}. In addition, the lack of clarity regarding whether the footwear were in direct contact with the cold ground may have further contributed to the observed deviation between simulated and measured temperatures.

Face and cheek skin temperature

We compared the model-predicted face (average of the nose and two earlobes) and cheek skin temperatures with the corresponding experimental data in *Studies* V1, V3, and V5, which were the only validation studies that

reported face or cheek skin temperature. Overall, the model predictions followed the trends of the experimental data in each of the three studies, with RMSEs ranging from 2.1 to 2.7 °C. In *Study V1*, the model captured the exponential-like decrease in face skin temperature (solid black line), closely matching the experimental data (solid black circles) throughout the cold-exposure period (Fig. 1D), yielding a RMSE of 2.6 °C with all predictions falling within two SEM of the measured values. At the end of the cold-exposure period, we observed a difference in temperature of 3.1 °C between the experimental data and the predicted value. For *Study V3*, which involved three distinct phases, the model performed reasonably well in predicting the cheek skin temperature in all three exposure phases (Fig. 3C), yielding an overall RMSE of 2.1 °C and 56% of the predictions falling within two SEM of the measurements. Specifically, the difference between the experimental data and the model prediction was 1.0 °C at the end of the cold-exposure phase (65 min) and 2.4 °C at the end of the rewarming phase (105 min). In *Study V5*, we also validated the model's predictions for the cheek against experimental data collected during a 60-minute cold-air exposure at an air temperature of −15.0 °C and a wind speed of 3.0 m·s^{−1}, with subjects in a standing posture. Figure 5D shows that the simulation yielded a faster decrease in cheek skin temperature compared to the experimental measurements, with a RMSE of 2.7 °C and none of the predictions falling within two SEM of the measurements. At the end of the cold-exposure period, we observed a difference in temperature of 3.2 °C between the experimental result and the model prediction. This discrepancy is likely due to the warmer initial cheek skin temperature value at time zero in the simulations as compared to the experimental data (36.1 °C versus 32.8 °C), which resulted in a larger gradient with the air temperature and a faster drop in skin temperature.

Discussion

The objective of this study was to extend our previously developed, anatomically realistic, 3-D whole-body virtual human thermoregulatory model to more comprehensively predict changes in core body temperature and skin temperatures (mean whole body, dorsum hand, fingertip, face, cheek, dorsum foot, and toe-tip) under extreme cold-stress conditions for an average U.S. male. We then validated the model predictions using 75 unique subjects from eight different studies for ambient air temperatures of −40.0 to 12.0 °C and wind speeds ranging from 0.1 to 3.0 m·s^{−1} (*Studies V1–V8*, Table 2). In these studies, the subjects either maintained a sitting posture, rested in the supine position, or maintained a standing posture, with all postures corresponding to an activity intensity of 0.9 MET. As the metric to assess the model's performance, we used the RMSE between relative changes in model-predicted temperatures and the corresponding experimental measurements, as well as the fraction of model predictions that fell within two SEM of the experimental data throughout the entire study.

Currently, there are no agreed-upon standards to evaluate the performance of thermoregulatory models or thresholds to define “acceptable” prediction errors, with some groups using an error threshold of ≤0.5 °C for T_{c} ⁵ and others using thresholds of ≤1.6 °C⁵ or ≤3.0 °C⁴² for T_{sk} . In the absence of standard thresholds, we defined as “acceptable” predictions those with RMSEs of ≤0.2 °C for T_{c} , ≤0.6 °C for $T_{\text{sk,m}}$, and ≤1.9 °C for fingertip, toe-tip, or cheek skin temperatures, which we determined by averaging the SEM across the corresponding validation studies considered in this work. In a replication study, we expect that 95% of the data would fall within two SEM of the experimental data. Across the eight validation studies, 7 out of 8 met the acceptable threshold for T_{c} , 2 out of 4 for $T_{\text{sk,m}}$ and fingertip skin temperature, 1 out of 3 for toe-tip, and none out of 3 for cheek skin temperature. Nevertheless, we observed a reasonable agreement between the model predictions and the experimental data for each of the eight studies, with RMSEs ranging from 0.5 to 1.8 °C for $\Delta T_{\text{sk,m}}$, 1.6 to 2.7 °C for fingertip, 1.3 to 1.5 °C for dorsum hand, 1.2 to 3.5 °C for toe-tip, 0.2 to 1.2 °C for dorsum foot, and 2.1 to 2.7 °C for cheek skin temperature changes. For ΔT_{c} , the model predictions resulted in an average RMSE of 0.2 °C, which met the acceptable threshold and implied that, in general, one cannot distinguish between the experimental measurements and the T_{c} predictions.

We reported temperature changes relative to time zero rather than absolute values due to the variability in core body temperature and skin temperature measurements across the different experimental studies at time zero. The body temperature at the start of an experiment can vary substantially within the same anatomical region across studies because of individual physiological factors, such as blood perfusion, thermal resistance, and body fat percentage⁴³. Inter-individual variability is further exacerbated by the small sample size of studies in extreme cold; in our case, the sample size ranged from 6 to 15 (Table 2). In the analyzed studies, the core body temperature across the eight studies (*Studies V1–V8*) at baseline (time zero) varied from 36.9 to 37.4 °C, whereas skin temperatures varied from 25.0 to 33.0 °C for the cheek (*Studies V3* and *V5*), 31.0 to 35.0 °C for the fingertip (*Studies V3* and *V4*), and 25.0 to 33.0 °C for the toe-tip (*Studies V2* and *V6*). Hence, we adopted this relative-change approach to minimize the influence of these variabilities and better capture the physiological trends and responses during cold exposure as compared to the model prediction.

We calibrated the model for the dorsum foot and toe-tip (*Studies C1–C3*), as well as the cheek skin (*Studies C4* and *C5*) regions using distinct experimental studies. The model calibration yielded RMSEs of ≤0.8 °C for the bare foot and ≤2.3 °C for the bare cheek regions. Nevertheless, for the five studies that measured foot-region temperature (Table 2), the model validation results yielded a wide distribution of RMSEs, ranging from 0.2 °C in *Study V5* to 3.5 °C in *Study V4*. We speculate that errors > 1.2 °C observed in *Studies V2* and *V4*, where the model underpredicted the temperature drop (Figs. 2C and 4D, respectively), were primarily due to uncertainties in the experimental set up, resulting in discrepancies between the inputs to the model and the actual experiment regarding the insulation of the footwear and socks as well as the potential contact of the sole of the footwear with the ground when subjects maintained a sitting posture. For example, the thermal insulation of cold-weather footwear (boots and mukluks) ranges from 1.3 to 2.4 clo^{44,45}, and those of socks range from 0.4 to 1.3 clo^{40,46}. However, because these studies did not provide the thermal resistance for the footwear and socks, we assumed a value of 2.0 clo for the entire mukluk ensemble, consisting of homespun wool socks and a mukluk footwear, which could have been larger than the actual value. In *Studies V2* and *V4*, the subjects maintained a sitting

posture, however, we assumed that the sole of the footwear was not in direct contact with the cold ground because this information was not reported in the original studies. During the experiments, the feet could have been supported by some physical apparatus, in contact with the ground, or hanging freely. In the absence of this important information, which is needed to define the boundary conditions in the model, we assumed that the feet were hanging freely and modeled heat loss from the foot to the surrounding cold air via convection. If in fact the footwear was in direct contact with the ground, conductive heat loss between the sole of the footwear and the cold ground would have yielded a larger decrease in foot temperature and a smaller RMSE. This was observed in *Study V6* (Fig. 6C,E), where we accounted for the conductive heat loss through the contact between the sole of the mukluk and the cold ground and obtained RMSEs for the dorsum foot and great toe-tip of 1.0 and 1.2 °C, respectively (Table 2).

In the extended model, we accounted for conductive heat losses from the plantar foot region through the sole of the footwear to the ground, as well as convective and radiative heat losses from the dorsum foot region. In this case, conductive heat transfer occurred when heat was exchanged through direct contact between the surface of a body segment and a colder surface, where the rate of heat transfer depended primarily on the thermal conductivity of the two surfaces. For subjects in a standing posture as in *Study V5*, conductive heat exchange was limited to the soles of the feet, which accounted for only 2.0 to 3.0% of the total body surface area. As such, its overall contribution to whole-body heat storage has largely been neglected in thermoregulatory models developed to date¹⁰, because this heat-transfer mechanism has a very small effect in the prediction of T_c . However, conductive heat transfer becomes relevant when the body segment we wish to predict is an extremity region, such as the hand or foot, in direct contact with a cold surface^{47,48}. To represent conductive heat transfer between the sole of the footwear and the ground, under cold exposure, we first performed an initial simulation to determine the temporal temperature profile at the bottom (sole) of the footwear. We assumed that initially the sole was at a thermoneutral temperature of 28.0 °C and in direct contact with a cold concrete surface at the ambient temperature reported in the corresponding experimental study (*Studies V3, V5, and V6*). Then, we predicted the temporal temperature profile at the sole and applied it as a boundary condition for the plantar foot region and used it in the simulation of these three experimental studies to capture the conductive heat loss that occurred when the bottom of the footwear was in direct contact with the cold ground. The accurate prediction of foot temperature in these studies highlights the importance of accurately characterizing the boundary conditions when a body extremity is in direct contact with a cold surface.

Our 3-D whole-body thermoregulatory model offers several benefits. First, it predicts temporal changes in temperature throughout the entire human body, beyond the limits of core and skin temperature measured in experimental studies. Second, it enables the simulation of exposures to extreme-cold environments, including temperatures as low as −40.0 °C. As such, the model provides an effective and practical alternative to human-subject experimentation, which is extremely difficult to conduct at very cold temperatures, and bypasses the challenges associated with recruiting human subjects and obtaining Institutional Review Board approval. This is particularly important for prolonged cold exposures typical of military operations, because experimental studies are limited to 3 h, as evidenced by the studies in Table 2. For example, we extended the exposure duration in *Study V5* from 60 min to 600 min (10 h) to investigate the body's response to a prolonged exposure to a frigid air temperature of −15.0 °C. Supplementary Figure S6 shows that, at the end of the 10-hour exposure, T_c had dropped by as much as 1.6 °C (panel A), $T_{sk,m}$ by 6.7 °C (panel B), and dorsum foot and cheek skin temperatures by 17.6 °C (panel C) and 14.3 °C (panel D), respectively, with the cheek skin temperature reaching a steady state after 6 h. Third, the virtual human model enables the development of Wind Chill Charts to estimate the exposure time that results in the onset of hypothermia and frostbite of the fingers^{29,31}, including the deterioration of hand dexterity and loss of tactile sensitivity as a function of environmental conditions (temperature and wind speed), clothing properties, and activity level representative of military field operations. For example, using 14.0 °C as the temperature threshold for the onset of deterioration in hand dexterity^{49,50}, the simulation for *Study V2* indicated that such a temperature drop would occur after 93 min of finger exposure at −25.0 °C, which closely matched the experimental data (91 min). Similarly, the simulation for *Study V3* indicated that a bare-hand exposure at −20.0 °C would result in a fingertip skin temperature drop to 14.0 °C after only 49 min, which showed adequate agreement with the ~58 min observed in the experiment. Overall, these results highlight the capability of the virtual human model to predict the risks of prolonged exposure to extremely cold air.

A direct comparison between the virtual human model and existing thermoregulatory models is challenging because such a comparison needs to be performed against the same experimental studies. However, none of the existing anatomically realistic models reported in the literature to date have been evaluated for studies in which the air temperature was below 0.5 °C, including our previous efforts^{10,12,14}. Moreover, some models have only been used to simulate very short exposures (~30 min)⁷ or have been evaluated for a single timepoint^{6,42}, precluding an assessment of the temporal evolution of skin and core body temperatures under extreme-cold conditions. Nonetheless, it is unlikely that predictions based on existing models will yield accurate results for extreme-cold temperatures because they do not incorporate key heat-transfer mechanisms and do not account for the spatial variation in blood temperature throughout the body and within the extremities. Previously, we demonstrated that omission of these modeling capabilities leads to underestimation of core body temperature by more than 1.5 °C during a 120-minute exposure at 1.0 °C¹². Improved accuracy, however, comes at the expense of increased computational costs. As described in Materials and Methods, a 60-minute simulation of the virtual human model required 27 h of CPU time. In contrast, the same simulation with a cylindrical model only required 5 min. However, as previously discussed, the additional computational cost of the virtual human model results in considerable improvements in prediction accuracy when compared to existing cylindrical models, including average lower errors in core temperature (0.1 °C vs. 0.3 °C) and whole-body mean skin temperature (1.1 °C vs. 2.4 °C), as well as better representation of shivering-induced heat production¹². Taken together, these

considerations highlight the benefits of the virtual human model, which despite its higher computational cost is better suited for applications requiring accurate, spatially detailed predictions under extreme cold-air conditions.

The population-average virtual human model is a useful tool for evaluating thermal responses and assessing risk of cold-related injuries at the population level. Although individualized predictions are important for injury prevention, particularly for susceptible individuals in the lower tail of the population distribution, the development of models to predict cold-related injuries at the individual level is challenging. This difficulty stems from the substantial between-individual variability in thermal responses due to factors such as differences in body composition, acclimatization status, and strength of certain thermoregulatory mechanisms, e.g., CIVID. As an alternative, population-average models provide a practical approach for risk assessment at the population level, while accounting for differences in susceptibility within the population. For example, as mentioned above, the virtual human model can be used to develop Wind Chill Charts to estimate the exposure time for finger frostbite at a given temperature. Thus, by defining a range of temperatures at which frostbite may occur in a population and their corresponding range of risk levels, say, 5% to 95%⁴, these charts generated with a population-average model can partially account for individual differences in the population.

Our model has limitations. First, the virtual human thermoregulatory model represents an average 50th percentile young, healthy U.S. male and does not account for anatomical and physiological individual and sex-based differences, including body fat content and its distribution⁵¹, hormonal influences on metabolic heat generation^{52–54}, and thermoregulatory differences in sweating^{55,56} and shivering rates^{53,57,58}. As such, the virtual human model is a population-based model and does not capture the full range of between-individual variability in thermal responses. Second, we validated the model for extreme cold-air exposures under sedentary conditions (sitting, lying, and standing posture), with all conditions corresponding to an activity intensity of 0.9 MET. Therefore, we did not evaluate the performance of the model under high activity levels. However, we are in the process of doing so for MET > 2.0, by representing the effect of sweat accumulation as a reduction in clothing insulation. As sweat accumulates with increased activity, water replaces the protective air layers within the clothing ensemble, reducing their effective insulation and enhancing conductive heat loss from the body to the environment⁵⁹. Moreover, here we showed that the model adequately represented thermal responses under sedentary conditions during extreme cold-air exposures as low as $-40.0\text{ }^{\circ}\text{C}$. In addition, we did not include cold-water immersion, however, we previously showed that the model is capable of predicting cold-water exposure down to $10.0\text{ }^{\circ}\text{C}$ ¹². Third, in developing the new correlation to represent the gradual rise in shivering metabolism, we were only able to find experimental studies with temperatures down to $-15.0\text{ }^{\circ}\text{C}$ with the necessary shivering data. However, despite the limited data availability, the model closely followed the experimental measurements for studies with air temperatures as low as $-40.0\text{ }^{\circ}\text{C}$, in which the model predictions of core body temperature were on average within $0.2\text{ }^{\circ}\text{C}$ of the measured data. Fourth, we could not validate the model predictions for wind speeds higher than 3.0 m s^{-1} because such data are not available in the open literature. This limitation is due to the difficulty in generating uniform and stable high wind speeds for long durations in large temperature-controlled environmental chambers used to conduct laboratory cold-exposure studies. Finally, we did not incorporate the potential effect of shivering fatigue^{60,61}, where heat generation due to shivering ceases when the core body temperature drops to $\sim 30.7\text{ }^{\circ}\text{C}$. However, in the studies analyzed here, even when we simulated a 10-hour exposure at $-15.0\text{ }^{\circ}\text{C}$, the core body temperature dropped by a maximum of $1.6\text{ }^{\circ}\text{C}$ (Supplementary Figure S6A), well above the threshold for shivering fatigue. This limitation may become important in the event of hemorrhagic shock, where a severe blood loss would reduce the body's heat capacity and impair thermoregulatory control. In such a scenario, the impaired heat production due to shivering would result in a further reduction in core body temperature and hypothermia-induced coagulopathy.

Conclusion

Here we extended and validated our 3-D virtual thermoregulatory human model so as to predict the spatiotemporal distribution of temperature throughout the body of an average young male resulting from cold-air exposure down to $-40.0\text{ }^{\circ}\text{C}$. Assessment of the model against experimental data from eight distinct studies demonstrated that the model could adequately predict core body temperature as well as skin temperatures of the cheek and the peripheral body regions, including the dorsum hand, fingertip, dorsum foot, and toe-tip. We anticipate that the model will help guide Service members to make informed decisions to help mitigate the risk of cold-related injuries, including frostbite and hypothermia, in austere cold environments.

Data availability

The predictions presented in this manuscript will be made available through a written request (including a summary of the planned research) to the corresponding author.

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Author contributions

M.S.: Conceptualization, Methodology, Software, Data curation, Visualization, Investigation, Writing-original draft, Writing-review & editing. L.A.: Software, Writing-review & editing. M.C.M.: Experiment, Writing-review & editing. M.R.S.: Experiment, Writing-review & editing. E.P.: Experiment, Writing-review & editing. S.L.: Experiment, Writing-review & editing. D.J.C.: Experimental protocol design, Conceptualization, Supervision, Project administration, Writing-review & editing. J.R.: Conceptualization, Supervision, Project administration, Writing-original draft, Writing-review & editing. J.E.R.: Conceptualization, Supervision, Writing-review & editing.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

The Institutional Review Board of the University of Connecticut (Storrs, CT, USA) and the U.S. Army Office of Human Research Oversight (Fort Detrick, MD, USA) approved *Study V6*. The modeling results presented herein were independently assessed for reproducibility.

Additional information

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