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Impact of an intermittent and localized cooling intervention on skin temperature, sleep quality and energy expenditure in free-living, young, healthy adults

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ABSTRACT

Where people live and work together it is not always possible to modify the ambient temperature; ways must therefore be found that allow individuals to feel thermally comfortable in such settings. The Embr Wave® is a wrist-worn device marketed as a 'personal thermostat' that can apply a local cooling stimulus to the skin. The aim of the present study was to determine the effect of an intermittent mild cold stimulus of 25 °C for 15–20 s every 5 min over 3.5 days under free-living conditions on 1) skin temperature, 2) perception of skin temperature, 3) sleep quality and 4) resting energy expenditure (REE) in young, healthy adults. Ten subjects wore the device for 3.5 consecutive days. This intervention reduced distal skin temperature after correcting for personal ambient temperature ($P < 0.05$), but did not affect the subjects' the perception of skin temperature, sleep quality or REE (all $P \geq 0.051$). Thus, this intermittent mild cold regime can reduce distal skin temperature, and wearing it under free-living conditions for 3.5 days does not seem to impair the perception of skin temperature and sleep quality or modify REE.

1. Introduction

The perception of the ambient temperature ('Standard 55 – Thermal Environmental Conditions for Human Occupancy', n.d.) is different in men and women (Karjalainen, 2012) and a link may exist between thermal comfort and health (Kilbourne, 1997; Lugo-Amador et al., 2004; Semenza et al., 1999). Some studies report that the perception of an uncomfortable ambient temperature may lead to sleep disturbances (Schellen et al., 2012), and may even be connected to sick building syndrome (Fisk and Rosenfeld, 1997). However, where people live, study and work together, the ambient temperature cannot often be 'individualized', which, given the above, might lead to health problems in some persons (Sheen et al., 2018).

Embr Labs Inc. markets a device designed to help one achieve personal thermal comfort under different ambient temperatures. This device, the Embr Wave® (https://embrlabs.com/), which has the form of an adjustable bracelet no bigger than a smart watch, has an aluminum plate that can be warmed/cooled to 25-42 °C at rates between 0.1-1 °C/sec as customizable intensities, frequencies, and durations. The consumer product was developed to allow individuals to leverage localized thermal stimulation on the wrist to change the wearer's perception of

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Abbreviations

ANOVA	Analysis of variance
BAT	Brown adipose tissue
BMI	Body mass index
CV	Coefficients of variance
ExpCo	Experimental condition
IS	Interdaily stability
IV	Intradaily variability
L10	mean wrist skin temperature for the 10 consecutive hours with the minimum values
M5	mean wrist skin temperature for the 5 consecutive hours with maximum wrist skin temperature values
Outdoor-AT	outdoor ambient temperature
Personal-AT	personal ambient temperature
RA	Relative amplitude
REE	Resting energy expenditure
RQ	Respiratory quotient
TL10	Time when L10 occurred
TM5	Time when M5 occurred
TRPM8	Transient receptor potential cation channel subfamily melastatin member 8
VAS	Visual analogue scale
VCO2	Volume of carbon dioxide
VO2	Volume of oxygen
WASO	Number and duration of periods spent awake after sleep onset

Table 1
Characteristics of study subjects.

	All (n = 10)	Women (n = 5)	Men (n = 5)
Age (years)	25.8 ± 3.2	27.4 ± 2.9	24.2 ± 2.8
Body mass index (kg/m^2)	23.0 ± 3.2	21.3 ± 2.1	24.7 ± 3.4
Fat Mass (kg)	21.0 ± 8.2	24.2 ± 9.6	17.8 ± 5.8
Fat Mass (%)	32.2 ± 9.5	33.2 ± 10.7	31.1 ± 9.3
Fat Mass Index (kg/m^2)	7.3 ± 2.5	8.1 ± 3.01	6.5 ± 1.9
Total Lean Mass (kg)	41.9 ± 11.3	45.6 ± 11.2	38.3 ± 11.2
Lean Mass Index (kg/m^2)	14.5 ± 2.5	15.2 ± 2.2	13.8 ± 2.8
Fat Free Mass (kg)	44.1 ± 11.7	48.1 ± 11.7	40.2 ± 11.5

Data are presented as means and standard deviations.

the ambient temperature and thus achieve greater thermal comfort (Wang and Luo, 2017). The consumer product has been shown to improve perceived temperature by over 3 °C (Wang et al., 2020) and has been found to offer sleep benefits to women experiencing disruptive night time hot flashes (Composto et al., 2019).

Over the last decade, it has been reported that short-term cold interventions (~10 days) might enhance the immune system and improve insulin sensitivity, among other factors (Stocks et al., 2001) in overweight individuals via the activation of different thermogenic tissues (Hanssen et al., 2015; Van Der Lans et al., 2015). Based on these findings, it has been suggested that the ambient temperature of buildings might be reduced to afford similar beneficial effects (Blauw et al., 2017; Martinez-Tellez et al., 2018). This however, is not really feasible; not everyone in a building feels comfortable at the same temperature. It has also been reported that, since sleep usually starts as core body temperature falls due to an increase in peripheral skin temperature in healthy subjects, manipulation of the skin temperature might modify sleep-onset latency (Kräuchi et al., 1999) and sleep quality (Acosta et al., 2019). Knowing what effect a local mild cold stimulus intervention under free-living conditions has on human health and sleep quality is not without clinical and public health interest. The overarching goal of the study was to evaluate the effects of intermittent and localized cold exposure (15–20 s every 5 min, applied only to 6.25 cm^2 of one wrist), on human physiology. This cold exposure is significantly more intermittent than the thermal stimulation used in previous studies with Embr Wave® (and is not currently available in the consumer product).

The aim of the present study was to determine the effect of an intermittent mild cold stimulus of 25 °C for 15–20 s every 5 min over 3.5 days under free-living conditions on 1) skin temperature, 2) the perception of skin temperature, 3) sleep quality, 4) resting energy expenditure (REE), and 5) the nutrient oxidation rate, in young healthy adults. This study represents a first investigation at the potential benefits of exposure to intermittent, localized cold sensations over prolonged periods of time.

Fig. 1. EMBR wave ® device placed on a wrist of a participant.

2. Material & Methods

2.1. Study subjects and ethics statement

The study subjects were 10 adults (5 women, 5 men; 25.8 ± 3.4 years; Table 1); all were healthy, non-smokers, who took no medication that might affect their thermoregulatory response to cold exposure and included from March to April 2019. The study protocol was designed in accordance with the latest version of the Declaration of Helsinki and approved by the Ethics Committee on Human Research of the University of Granada (no. 793/CEIH/2019). Informed consent was obtained from all subjects.

2.2. Embr Wave® device

Commercially available Embr Wave® devices were programmed to provide an intermittent cold stimulus, a ramp down to 25 °C for 15–20 s every 5 min (Fig. 1). This functionality was developed to deliberately test the potential benefits of intermittent mild cold stimulation beyond commercially available operating modes. Subjects were instructed to remove the device, which was worn on the right wrist, only for handwashing and bathing. Testing was performed on two subjects (one male, one female) per week.

2.3. Experimental procedure

The subjects worn the Embr Wave® device over a period of 3.5 days under free-living conditions.

2.4. Skin temperature measurements using iButtons

Skin temperature measurements were taken every 10 min using DS-1922 L Thermochron iButtons (resolution: 0.0625 °C) (Maxim, Dallas, USA) (Martinez-Tellez et al., 2019a), the validity and reliability of which have been established for the assessment of skin temperature in humans (Smith et al., 2010; van Marken Lichtenbelt et al., 2006). These were placed on the back of the hand, the inner part of the wrist, the forearm, in the supraclavicular area, and on the instep of both the right and left sides of the body. To measure the personal ambient temperature to which each subject was exposed (personal-AT), the subjects carried an iButton attached to a plastic fob on their person, though never in direct contact with their body or under clothing (Martinez-Tellez et al., 2018) (e.g., attached to a backpack or bag). Subjects were told to remove the iButtons only when bathing or washing their hands, and once finished, to put the iButtons on again by themselves; non-wear periods were recorded in a diary. All iButtons were programmed to start recording data every 10 min for 3.5 days, starting at 06:00 h on day 1. 24-hour means were determined, and overall 3.5-day means then determined using the Temperatus® software (http://profith.ugr.es/temperatus?lang=en) (Martinez-Tellez et al., 2019b). The control group was composed of the same subjects who received no intermittent mild cold stimulation for 3.5 days before the activation of the device.

2.5. Outdoor ambient temperature

To adjust for the effect of the mean outdoor ambient temperature (outdoor-AT), temperatures for the city of Granada, Spain (where this work was performed) were downloaded every day of the study period from the Spanish National Meteorological Agency (www.aemet.es/es/portada). The test and control period outdoor-AT and the personal-AT for each subject were then calculated.

2.6. Perception of skin temperature

The perception of skin temperature was assessed using a 100-long mm visual analogue scale (VAS), where 0 mm represented “not cold at all” and 100 mm the “maximum tolerable cold”. Subjects reported the perception of skin temperature over the different body sites (body, hands and feet) every day before they went to sleep (Lundgren et al., 2014).

2.7. Sleep quality

Sleep quality variables were determined as previously described (Ortiz-Tudela et al., 2010a; Witting et al., 1990) (a number of studies have shown that the wrist skin temperature provides a reliable proxy of sleep quality (Blazquez et al., 2012)). The interdaily stability (IS) of the wrist skin temperature (i.e., the constancy of the 24 h rhythmic pattern over the days of data collection), the intradaily variability (IV; i.e., the fragmentation of the rhythm), and the relative amplitude (RA) were determined as described elsewhere (Ortiz-Tudela et al., 2010b; Witting et al., 1990). The RA was determined as the difference between the mean wrist skin temperature for the 5 consecutive hours with the maximum wrist skin temperature values (M5), and the mean wrist skin temperature for the 10 consecutive hours with the minimum values (L10), divided by their sum (Martinez-Nicolas et al., 2011). Finally, the times at which L10 and M5 occurred (TL10 and TM5, respectively) were calculated as previously described (Martinez-Nicolas et al., 2011). The mean daily pattern for wrist skin temperature was calculated per individual, and then the mean determined for all subjects. The mean daily determined for the test and control groups.

The subjects also wore an ActiGraph GT3X + accelerometer (ActiGraph, Pensacola, FL, US) on their left wrist for the entire experimental period (except for water-based activities). The following sleep-related variables were determined using this device: (1) night onset (time at which the subject fell asleep); (2) wake-up time; (3) in-bed time (time between going to bed and waking up); (4) sleep duration (time between falling asleep and waking up); (5) sleep efficiency (ratio of sleep duration to in-bed time); (6) number and duration of periods spent awake after sleep onset (WASO). Daytime naps were not taken into account, and participants used a diary log for selecting sleeping periods. Before analysis, atypical data were eliminated and all non-wear time periods excluded. At least four valid days of data (i.e., each with >75% of the 100% possible data for a 24 h period) were required for a subject’s results to be included in analyses.

2.8. Resting energy expenditure and nutrient oxidation

REE and nutrient oxidation rates were measured on three occasions following procedures described elsewhere, and the latest recommendations (Alcantara et al., 2020; Fullmer et al., 2015a; Sanchez-Delgado et al., 2019). Briefly, REE was measured at 08.30 h every day (i.e., after the overnight fast) in a quiet room with dim lighting under controlled environmental conditions (22-24 °C; humidity 35–45%) (Fullmer et al., 2015b). The REE was assessed over 30 min using the Omnical metabolic cart equipped with a ventilated plastic-canopy for subject gases collection (Maastricht Instruments, Maastricht, Netherlands) previous a resting period (20 min). This cart has been previously validated for REE and nutrient oxidation rate determinations (Kaviani et al., 2018; Schoffelen et al., 2019). The calibration of the flow and gases analyzers was performed automatically before each measurement. The gas data returned were averaged for every minute using an Excel spreadsheet (the first 5-min of measurement were discarded) (Fullmer et al., 2015b). The coefficients of variance (CV) of VO_2, VCO_2 and RQ were then calculated. A 5-min period that met the steady state criteria of CV<10% for VO_2 and VCO_2, and CV<5% for RQ was then selected for data analysis (Alcantara et al, 2018, 2020; Sanchez-Delgado et al., 2018). Lastly, using the same selected data period, and assuming zero urinary nitrogen excretion, the REE was estimated using Weir’s equation (WEIR, 1949), carbohydrate and fat oxidation rates were estimated using Frayn’s equation (Frayn, 1983), and the respiratory quotient (RQ; VCO_2/VO_2) calculated.

2.9. Body composition

Subject weight and height (barefoot and wearing standardized light clothes) were determined using a model 799 SECA scale and stadiometer (SECA, Hamburg, Germany). Body mass index (BMI) was calculated as weight/height squared (kg/m^2). Body composition was measured by dual energy X-ray absorptiometry using a Wi Discovery device (Hologic, Inc., Bedford, MA, USA). Lean and fat mass indices were calculated as lean mass/height squared and fat mass/height squared (kg/m^2).

2.9.1. Statistical analysis

Results are presented as means ± standard deviation, unless otherwise stated. General mixed model ANOVA was used to examine whether skin temperature and the perception of skin temperature differed under the test and control conditions. ‘Time’ (days 1, 2 and 3) was deemed to be a ‘within-subjects’ factors, whereas control and experimental conditions were regarded as ‘between-subject’ factors. Means were calculated for all iButtons daily temperatures, VAS perceptions of skin temperature, sleep quality variables, REE and the nutrient oxidation rate for the 3.5 days, and one-way ANOVA performed to examine the differences between the test and control conditions. To take into account possible confounders, REE/lean body mass ratio, and skin temperature outcomes/personal-AT ratios were determined and compared between

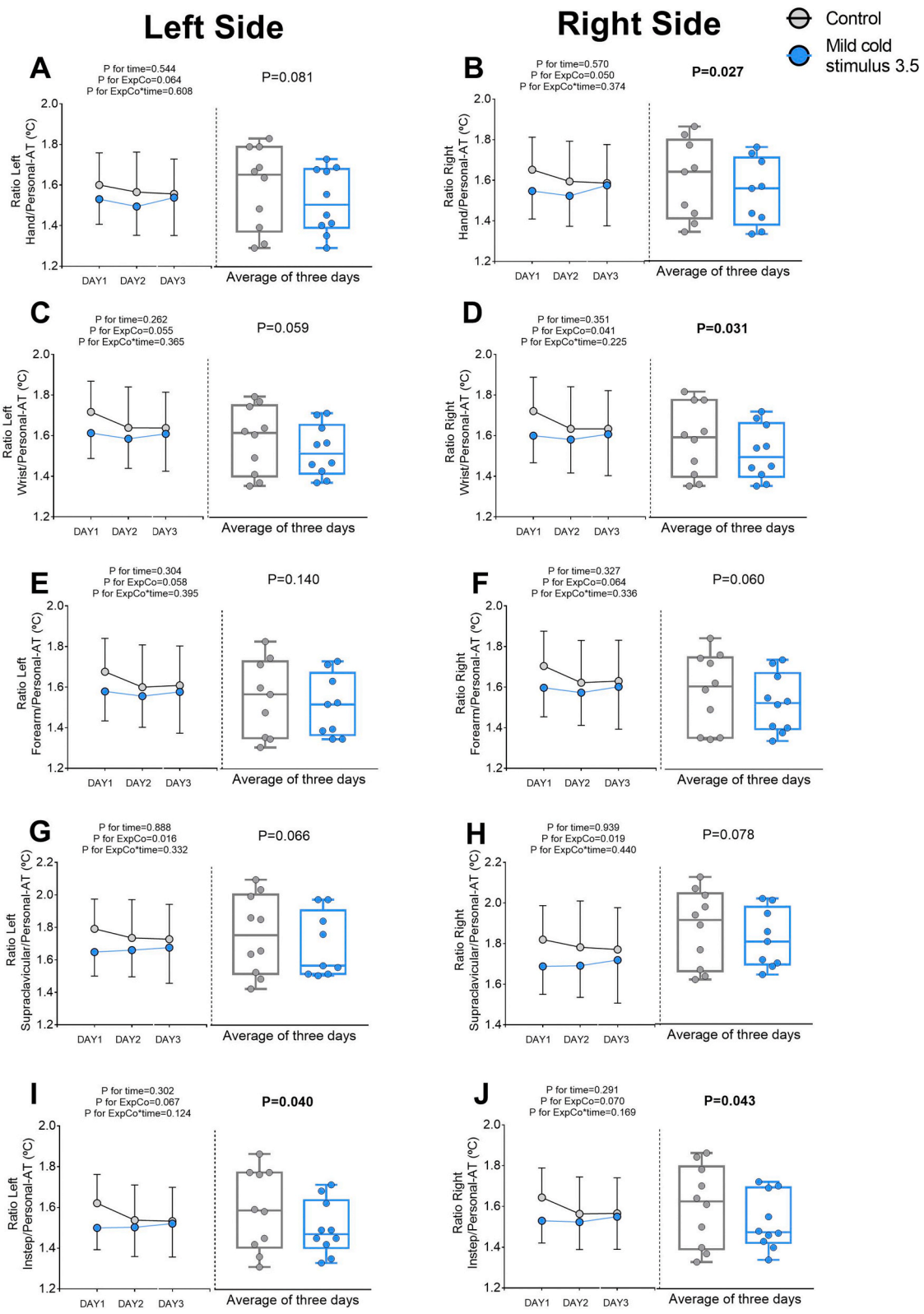

Fig. 2. Effect of the 3.5-day intermittent mild cold stimulus on skin temperature (as measured by iButtons). Two-way ANOVA was used to detect differences between the experimental (blue lines) and control (grey lines) conditions. One-way ANOVA was used to determine whether the mean skin temperature in the experimental conditions (blue boxes) and control conditions (grey boxes) differed. Data used in two-way ANOVA are presented as means and 95% confidence intervals, whereas those for one-way ANOVA are presented as means and minimum to maximum ranges. All data are adjusted for personal ambient temperature (personal-AT). Skin temperature was quantified on the left and right hands (A and B), left and right wrists (C and D), left and right forearms (E and F), left and right supraclavicular (G and H), and left and right insteps (I and J). ExpCo = experimental condition.

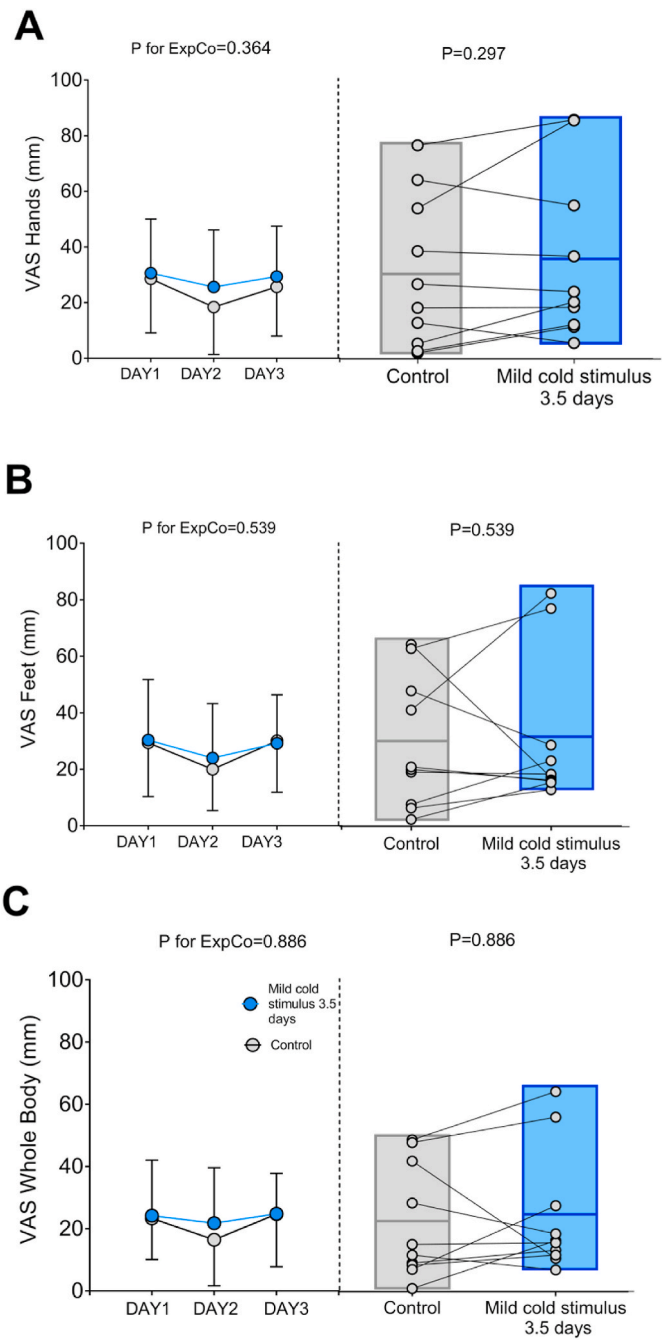

Fig. 3. Effect of the 3.5-day intermittent mild cold stimulus on the perception of skin temperature, measured using a visual analogue scale (VAS), where 0 mm represented "not cold at all" and 100 mm the "maximum tolerable cold". Two-way ANOVA was used to detect differences between the experimental (blue lines) and control (grey lines) conditions. One-way ANOVA was used to determine whether the mean skin temperature in the experimental conditions (blue boxes) and control conditions (grey boxes) differed. Data used in two-way ANOVA are presented as means and 95% confidence intervals, whereas those for one-way ANOVA are presented as means and standard deviations. ExpCo = experimental condition.

the control and test conditions using one-way ANOVA with *post hoc* Bonferroni correction. All calculations were made using the Statistical Package for the Social Sciences v.21.0 (IBM Corporation, Chicago IL, USA). Significance was set at $P < 0.05$. All figures were created using GraphPad Prism v.7.00 software (GraphPad Software, La Jolla, CA, USA).

3. Results

3.1. Effect of an intermittent cold regime on skin temperature

Fig. S1 shows that outdoor-AT varied slightly over the study period, whereas the personal-AT was constant. Thus, when outdoor-AT decreased, personal-AT remained stable. Moreover, the outdoor-AT data show the temperature of the first day of the intervention to be different compared to the remaining days (Fig. S1). The main analyses were performed performing a ratio with personal-AT only (Fig. 2).

During the 3.5-day test condition period, the distal skin temperatures tended to be lower during the first 10 h, although not significantly so (data not shown), nor was it maintained. The 3.5-day means for the skin temperatures of the *right* hand, wrist and instep were lower than under control condition (Fig. 2B, D and J; $P = 0.027$, $P = 0.031$ and $P = 0.043$ respectively). The skin temperature of the *left* instep was also lower (Fig. 2I; $P = 0.040$). No significant differences were seen for the *left* supraclavicular area (Fig. 2A, C, E, F, G and H; all $P \geq 0.059$). When analyses were not adjusted for personal-AT, none of the above effects were apparent (see Fig. S2; all $P \geq 0.112$).

3.2. Effect of an intermittent cold regime on perception of skin temperature

Fig. 3 shows that the 3.5-day intermittent mild cold stimulus did not modify the perception of skin temperature anywhere before sleeping (Fig. 3A, B and C; all $P \geq 0.297$).

3.3. Effect of an intermittent cold regime on sleep quality

The M5 for the left and right wrists was significantly higher during the time of the intermittent mild cold stimulus regimen (Figs. S3E and F; both $P \leq 0.005$), although these differences disappeared after adjusting for personal-AT (Fig. 4E and F; both $P \geq 0.124$). This suggests that ambient temperature is an important confounder of any quantification of the change in sleep quality that might be thought due to the stimulus provided by the device. The results returned by the accelerometers also suggested the stimulus had no significant effect on total sleep, sleep-onset times (Table S1; both $P \geq 0.483$) or sleep efficiency (Table S1; $P = 0.61$).

3.4. Effect of an intermittent cold regime on REE and nutrient oxidation rate

The stimulus had no effect on REE, REE/lean body mass ratio, or the nutrient oxidation (carbohydrate and fat oxidation) rate (Fig. 5A, B, C and D; all $P \geq 0.485$). This lack of effect was observed even when using gas exchange data selection criteria different (i.e., Time Interval instead of steady state method) to those explained in Methods (data not shown).

4. Discussion

The present results show that an intermittent mild cold stimulus regimen - 25 °C for 15–20 s every 5 min over 3.5 days reduces the distal skin temperature, but it does not impair the perception of skin temperature and sleep quality, or modify REE and the nutrient oxidation rate.

The reduction in distal skin temperature - on both the left and right sides - caused by the 3.5 days stimulus regimen suggests the device might stimulate TRPM8 (transient receptor potential cation channel subfamily melastatin member 8) in the wrist area. Information would then be sent to the hypothalamus that the hand was being cooled down, leading to peripheral vasoconstriction (Dhaka et al., 2007; Flor-ez-Duquet and Mcdonald, 1998) in an attempt to preserve the core body temperature. Different studies suggest that thermoregulatory responses occurring simultaneously on both sides of the body when only one side has been stimulated, might be a reflection of better cardiovascular

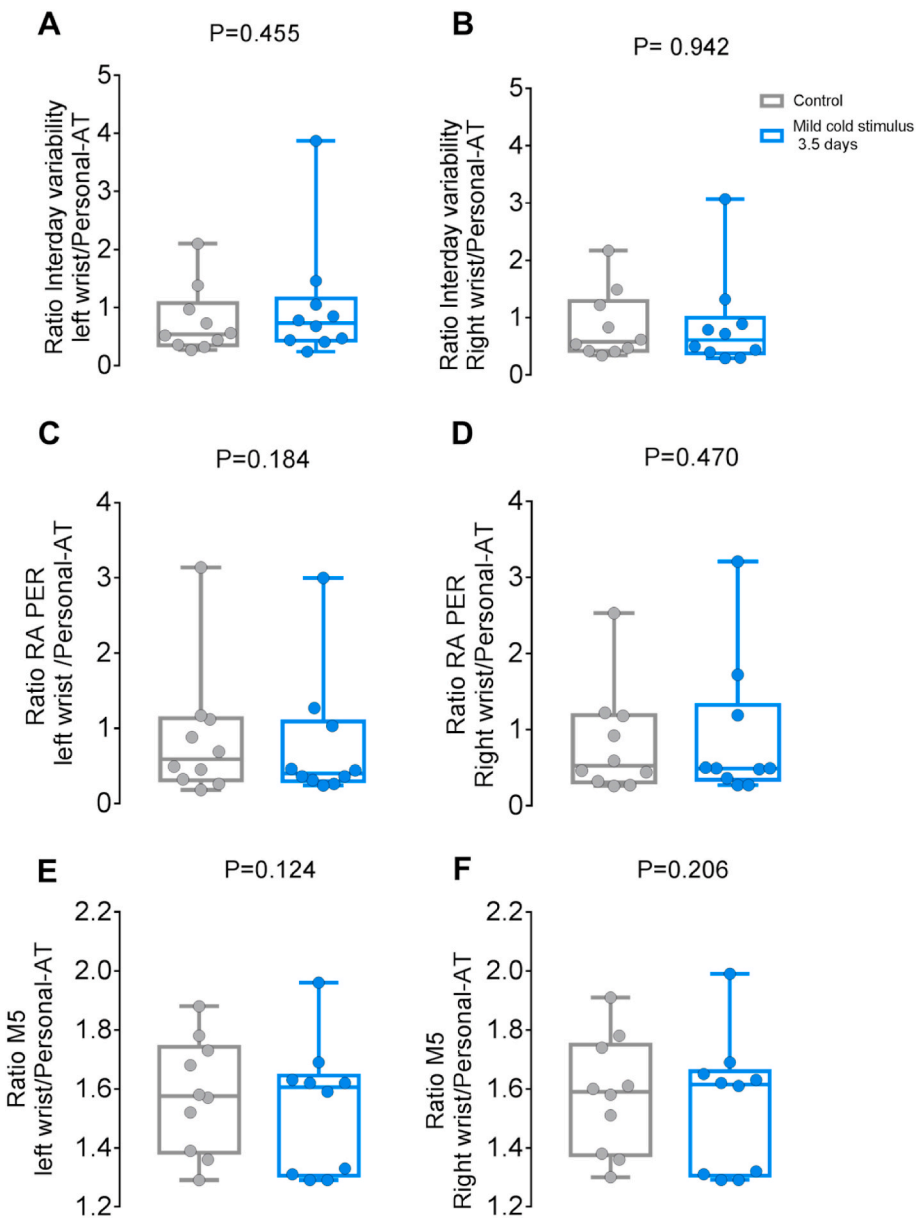

Fig. 4. Effect of the 3.5-day intermittent mild cold stimulus on sleep quality. One-way ANOVA was used to study identify differences in sleep quality variables between the control (grey boxes) and experimental conditions (blue boxes). Data used in one-way ANOVA are presented as means and minimum to maximum ranges. All data are adjusted for personal ambient temperature (Personal-AT). Intradaily variability was quantified for the left and right wrist (A and B), as was relative amplitude (RA) (C and D), and M5 (E and F). Two-way ANOVA was used to detect differences between the experimental (blue lines) and control (grey lines) conditions.

health (Alba et al., 2019; Kim et al., 2019; Maeda, 2017).

Additionally, the fall seen in the distal skin temperature over the initial 10 h of monitoring was not maintained, suggesting a physiological or behavioral adaptation to the intermittent mild-cold stimulus took place. This might also explain the lack of any change in the perception of skin temperature, REE or the nutrient oxidation rate. Future work might investigate whether different cold stimulus regimens are also induce such adaptation (Castellani and Young, 2016). Moreover, skin temperature values were shown as a ratio to the Personal-AT due to the huge intraindividual variability observed (Fig. S1B). Surprisingly, we found that *right* distal skin temperatures (where the device was placed), were lower in comparison to *left* distal skin temperatures. This finding suggests that the effect of the device on distal skin temperature was independent of the Personal-AT, however, further and better studies are needed to confirm this hypothesis.

It was initially thought that the 3.5-day intermittent mild cold stimulus might impair sleep quality. However, no such effect was seen, perhaps again due the above-suggested physiological adaptation to the stimulus. Moreover, none of the present subjects had sleep or thermoregulatory problems; it remains to be seen whether an intermittent cold regime modifies sleep patterns in those with poorer sleep and thermoregulatory health (Słomko et al., 2018).

Brown adipose tissue (BAT) is one of the thermogenic tissues activated by cold (Ruiz et al., 2018). In the present study, the supraclavicular skin temperature was measured by thermal imaging as a proxy of BAT activity, which validity has not been proven yet (Jimenez-Pavon et al., 2019). However, current evidence suggests that the supraclavicular skin temperature should be interpreted as the outcome of the combined responses of the blood vessels, skeletal muscles and BAT (Jimenez-Pavon et al., 2019). In any event, the supraclavicular skin temperature remained unaltered, suggesting that 3.5 days intermittent mild cold regimen to be insufficient to activate thermogenic responses. Further research to determine whether the intermittent mild cold exposure activates human BAT when applied to different locations on the body or with different frequencies, intensities or durations is warranted.

4.1. Limitations

The present results should be interpreted with caution since the

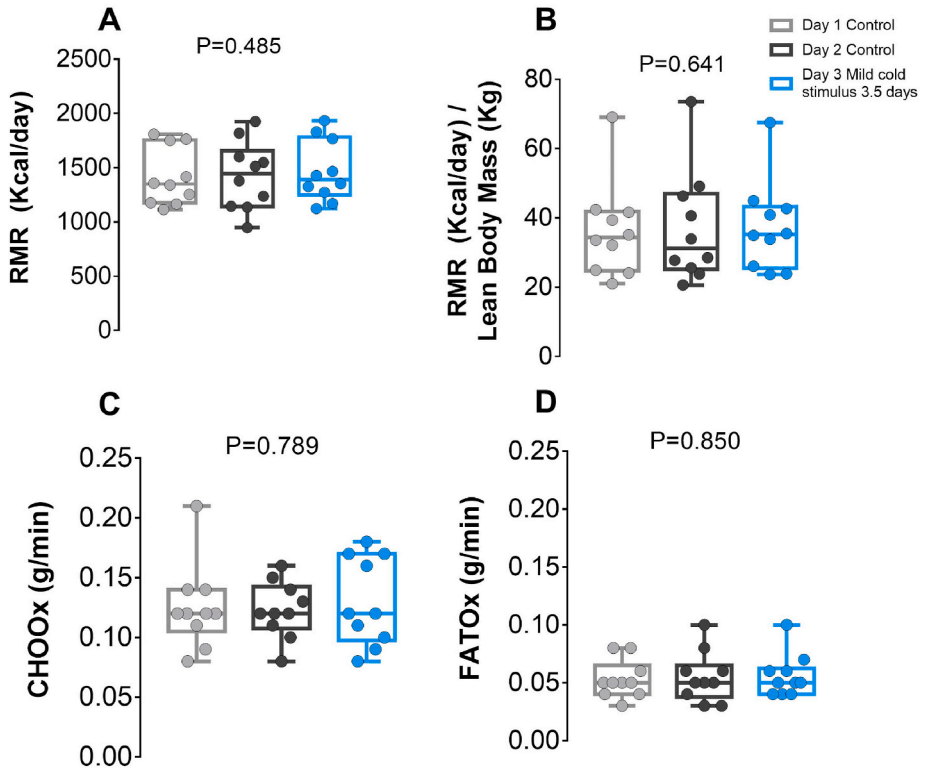

Fig. 5. Effect of the 3.5-day intermittent mild cold stimulus on resting energy expenditure (REE) and nutrient oxidation as measured by indirect calorimetry. Two-way ANOVA was used to detect differences between the experimental (1 day, blue boxes blue lines) and control (2 days, grey and black boxes) conditions. REE was expressed as kilocalories per day (A) and as a ratio (REE/lean body mass; B). Nutrient oxidation was estimated for carbohydrates (C) and fats (D).

sample was small, although it was homogeneous in terms of age and health and body weight adequacy; but the extrapolation of these results to other populations would be unwise. The intermittent and localized cooling stimulation regime was designed as an initial test of extremely mild cold exposure, and not developed for targeted physiological responses. Further, the cold stimulus was not individualized with respect to thermal sensitivity, meaning it felt differently to different subjects. The thermoneutral zone and whether the participants were exposed to indoor or outdoor during the study days were not recorded in the current study. The duration of the intervention was a continuous 3.5 days of stimulation every 5 min - apparently long enough for physiological or behavioral adaptation to occur, although longer, colder, or less continuous interventions might return different results. Finally, the personal-AT of the subjects tended to change at the moment the Embr Wave® device was switched on. This might indicate that wearing the device led the subjects to seek out warmer environments. Future work should determine whether a causal relationship exists.

5. Conclusion

This study shows that an intermittent and localized mild cold stimulus provided over 3.5 days reduces distal skin temperature but does not induce a measurable modification of the perception of skin temperature, sleep quality, REE, or the nutrient oxidation rate in this cohort.

Authors' contributions

Conception and design of the research: HX, AMN and BMT. HX and WDMA performed the experiments. HX, AMN, FMA, JMAA, DJP, JCP and BMT analyzed the data. HX, FMA, AMN, DJP, JCP, JRR and BMT interpreted the results. HX and BMT prepared the figures and drafted the manuscript. HX, WDMA, JMAA, FMA, AMN, DJP, JCP, JRR and BMT critically revised the manuscript and approved the final version.

Declaration of competing interest

Embr Labs Inc. provided the devices used in this work, but the company did not participate in the design of experiments, the interpretation of the data, or the drafting of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtherbio.2021.102875.

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