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**Title:** Oral L-Menthol reduces thermal sensation, increases work-rate and extends time to exhaustion, in the heat at a fixed rating of perceived exertion

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**Running head:** "Menthol exercise tolerance in heat"

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**Abbreviations:**

HR = Heart rate
R$f$ = Respiratory frequency
RPE = Rating of perceived exertion
TRAAK = TWIK-related arachidonic acid-stimulated K$^+$ channel
TREK-1 = TWIK-related K$^+$-1 channel
TRPM8 = Transient receptor potential cation channel subfamily M member 8
VE = Minute ventilation
$\dot{V}O_2$ = Oxygen consumption
VT = Tidal volume
Wmax = Power output at $\dot{V}O_{2max}$

**Abstract**

Purpose
The study investigated the effect of a non-thermal cooling agent, L-Menthol, on exercise at a fixed subjective rating of perceived exertion (RPE) in a hot environment.

Method
Eight male participants completed two trials at an exercise intensity between 'hard' and 'very hard', equating to 16 on the RPE scale at ~ 35 ºC. Participants were instructed to continually adjust their power output to maintain an RPE of 16 throughout the exercise trial, stopping once power output had fallen by 30 %. In a randomised crossover design, either L-Menthol or placebo mouthwash was administered prior to exercise and at 10 min intervals. Power output, $\dot{V}O_2$, heart rate, core and skin temperature was monitored, alongside thermal sensation and thermal comfort. Isokinetic peak power sprints were conducted prior to and immediately after the fixed RPE trial.

Results
Exercise time was greater (23:23 ± 3:36 *vs.* 21:44 ± 2:32 min; $P = 0.049$) and average power output increased (173 ± 24 *vs.* 167 ± 24 W; $P = 0.044$) in the L-Menthol condition. Peak isokinetic sprint power declined from pre-post trial in the L-Menthol l (9.0 %; $P = 0.015$) but not in the placebo condition (3.4 %; $P = 0.275$). Thermal sensation was lower in the L-Menthol condition ($P = 0.036$), despite no changes in skin or core temperature ($P > 0.05$).

Conclusion
These results indicate that a non-thermal cooling mouth rinse lowered thermal sensation, resulting in an elevated work rate, which extended exercise time in the heat at a fixed RPE.

**Introduction**


The nature of impaired exercise performance in the heat is multifactorial, incorporating an interplay of physiological, mechanical and psychological mechanisms (Galloway and Maughan 1997; Marino et al. 2000; Tucker et al. 2004; Nybo 2008). Increases in perceived exertion correlate with rising core temperature during active and passive heating (Galloway and Maughan 1997; González-Alonso et al. 1999; Armada-da-Silva et al. 2004; Crewe et al. 2008) and have been linked to changes in skin temperature (Cabanac et al. 1971; Cabanac and Massonnet 1972; Crewe et al. 2008; Flouris and Cheung 2009; Schlader et al. 2009; Schlader et al. 2011a), which initiate thermoregulatory behaviour to defend homeostasis. During self-paced exercise in the heat, perception of effort is thought to drive thermo-behavioural adjustments in work-rate (Tucker et al. 2004; Tucker et al. 2006), owing to an increased thermal load and, thus, greater homeostatic challenge. Indeed, exercise in the heat induces a greater variability in self-paced power production (Peiffer and Abbiss 2011), anticipatory reductions in total workload prior to exercise (Tucker et al. 2004; Tucker et al. 2006) and a variety of other impairments to performance (MacDougall et al. 1974; Galloway and Maughan 1997; Tatterson et al. 2000; Nybo and Nielsen 2001).


A number of thermal pre-cooling strategies, which lower core body temperature, thereby increasing the capacity for heat storage, have been successful in improving exercise performance. For example, strategies such as cold water immersion (Marino and Booth 1998), cooling garments (Arngrïmsson et al. 2007), face cooling (Armada-da-Silva et al. 2004) and ice slurry ingestion (Vanden Hoek et al. 2004; Siegel et al. 2010; Ross et al. 2011) have been described. Yet whilst changes in thermoregulatory behaviour during exercise in the heat have been more closely associated with thermal cooling, there is increasing evidence that non-thermal cooling methods can also facilitate behavioural modification (Schlader et al. 2011b). A reduction in thermal sensation, independent of skin temperature, was achieved by topical application of an aromatic non-thermal cooling L-Menthol gel to the face, which facilitated an increase in workload in the heat (Schlader et al. 2011b). Application of menthol spray to a cycling jersey also initiated improvements in thermal comfort but did not improve 40 km time trial performance (Barwood et al. 2012).


When administered orally, L-Menthol enhances cold sensations in the mouth (Eccles 1994) and inhibits the perception of warmth (Green 1986). Furthermore, L-Menthol mouth rinse has been shown to increase cycling time to exhaustion by ~9 % (Mündel and Jones 2010) and improve 5 km running performance by ~3 % (Stevens et al. 2015; Stevens and Best 2016) when performed in high ambient temperatures (33-34 ℃). Despite the growing evidence to support the ergogenic effects of L-Menthol mouth rinse when administered to athletes in thermally challenging environments, its effect on perceived exertion and, thus, conscious regulation of exercise intensity in the heat has not been specifically addressed. Mechanistically, L-Menthol acts on thermoreceptors on the oral mucosal surfaces (Eccles 1994) and is primarily transduced by a voltage-gated ion channel, TRPM8, on peripheral sensory nerve fibres (McKemy et al. 2002; Peier et al. 2002; Andersen et al. 2014). Sensory information is then communicated to the thalamus and onwards to the somatosensory cortex (Andersen et al. 2014).

The Borg RPE scale (Borg 1982) is commonly used to evaluate exercise intensity but, more recently, has been identified as a regulator of exercise intensity (Tucker et al. 2006). Factors that determine RPE are thought to be multifaceted and include the central integration of perceptual, peripheral and environmental sensory cues (Hampson et al. 2001). Integration of these sensory cues during exercise in the heat elicits an increase in RPE (Nybo and Nielsen 2001; Tucker et al. 2004), which is characterised by high thermal load, as well as acute metabolic, cardiovascular and hormonal perturbation (Galloway and Maughan 1997; Nybo 2008). To investigate the distinct roles of thermal sensation and skin/body temperature on thermo-behaviour, a fixed RPE 'clamp' protocol (Tucker et al. 2006) has previously been developed. The RPE clamp protocol instructs participants to adjust their work-rate such that perceived exertion between 'hard' and 'very hard', equivalent to 16 on the Borg RPE scale, is maintained. Using this protocol in thermoneutral and hot ambient conditions, Tucker et al. (2006) identified that an increased rate of heat storage observed in the hot trial led to a greater reduction in exercise duration and a decline in integrated EMG activity. This method has also been used to evaluate the role of centrally (Swart et al. 2009) and peripherally-acting (Browne and Renfree 2013) drugs on exercise-induced fatigue. This protocol could therefore be extended to explore the role of non-thermal cooling agents, particularly those with an established influence on sensory pathways, on perceived effort during exercise in the heat.

Therefore, the main purpose of this study was to investigate the effects of the non-thermal cooling agent, L-Menthol, on exercise performance in the heat using a fixed RPE protocol. We hypothesized that administration of L-Menthol would lead to an increased sense of oral coolness, facilitating a higher work rate at a fixed perceived effort and subsequently increase cycling duration in a hot environment.

**Materials and methods**

**Participants**

Eight male non-acclimated participants (age = 26 ± 5 years; body mass = 77.1 ± 15.3 kg; stature = 178.4 ± 4.8 cm; Σ7 skinfold 52.3 ± 20.7 mm; maximal oxygen uptake, $\dot{V}O_{2max}$ = 55.4 ± 6.0 ml/min/kg), with a minimum of 5-h general fitness training per week, consented to take part in this study. None of the participants had visited a hot country in the previous three months and all resided in the UK. Participants were instructed to avoid consumption of alcohol or caffeinated products for 24-h before each visit, as well as strenuous exercise 48-h before testing and to arrive fully hydrated. Ethical approval was provided by St Mary's University ethics committee, which was conducted in accordance with the 1964 Helsinki declaration.

**Study design**

A randomised, single-blind, crossover design was adopted to examine the effect of L-Menthol mouth rinse on exercise tolerance in the heat using a fixed RPE protocol (Tucker et al. 2006). Randomisation was conducted by generating random numbers for each condition for all participants using online software (Urbaniak and Plous 2015). Participants were blinded to the original hypothesis of the study and informed that the effect of differing mouth rinses on exercise in the heat was being investigated. Participants visited the Laboratory on four separate occasions, each separated by at least 72-h. During visit 1, participants conducted baseline testing to establish maximal oxygen uptake ($\dot{V}O_{2max}$) and power output at $\dot{V}O_{2max}$ (Wmax). During visit 2, participants undertook a full mock experimental trial and were familiarized with the equipment used in the heat chamber. During visits 3 and 4, the participants completed the fixed RPE protocol either with L-Menthol mouth rinse or placebo, completing their next trial 72-h later.

**Experimental procedures**

*Preliminary testing*

Participants reported to the laboratory to conduct preliminary testing consisting of anthropometric measurements and an incremental ramp test. Skinfold thickness was assessed at seven sites namely: biceps, triceps, subscapular, supraspinale, abdominal, front thigh and medial calf. Measures were taken in duplicate to the nearest 0.1 mm using skinfold calipers (Harpenden, Burgess Hill, UK) and summed to generate a sum of skinfold (Σ7) measure. Participants then performed a self-paced warm-up for 10-min and were asked to select a preferred cadence that was standardised throughout the remaining experimental trials. The incremental ramp test began at 100 W, and workload increased in one-min stages at a rate of 25 W/min until volitional fatigue. All testing was conducted on an electronically-braked cycle ergometer (Lode Excalibur Sport, The Netherlands). Oxygen uptake was measured using a telemetric portable gas analyser (CosMed K4b2 Portable, Rome, Italy). RPE was measured at the end of each 1-min stage by pointing to a 15-grade RPE scale held by an investigator. Following the incremental ramp test, two familiarisation exercises were conducted, which were subsequently used with the intention of calibrating the participant's RPE-based selection of power output in the main trials. In

the first exercise, participants conducted incremental ramp steps in accordance with the power output / RPE relationship derived from the incremental ramp test. The steps followed the order: RPE 11 for 4 min, RPE 13 for 3 min, and RPE 15 for 2 min. Participants were blinded to the RPE and asked to rate their own RPE to aid familiarisation with the RPE scale. The second exercise began at 110 W and involved participants controlling resistance on the ergometer, whilst being blinded to actual power output, in order to achieve an RPE they perceived as equalling RPE-16 over a period of 5 min. The latter test was used to demonstrate the reliability of the participant's ability to select a replicable exercise intensity at the desired RPE across the familiarisation, and two experimental trials in the heat (34.8 ± 1.0 ºC) prior to administration of the mouth rinse (Table 1).

*Familiarisation trial*

Full familiarisation trials, replicating the experimental conditions were then conducted in an environmental heat chamber, instructing participants of how to perform the experimental tests, to experience heat stress and to reduce a subsequent learning effect. Participants were also given significant time to discuss and understand the RPE protocol with the researchers both before and after this initial familiarisation performance trial.

*Experimental trials*

Participants performed two randomised experimental trials, separated by 72-h in an environmental heat chamber in temperatures of 35.0 ± 0.8 ºC, relative humidity 47.8 ± 2.3 %. For each participant, the experimental trials were conducted at the same time of day to eliminate the effect of circadian variation. Euhydration was established by identifying urine osmolality < 715 mOsm/Kg $H_2O$ (Shirreffs and Maughan 1998) (Pocket Osmochek, Vitech Scientific Ltd, West Sussex, UK) average hydration was 376.5 ± 188 mOsmols/kg $H_2O$, across both conditions. Participants rested for 30-min and baseline measures were recorded prior to entering the environmental heat chamber. Upon entering the heat chamber, the participants conducted two standardised warm-up procedures as outlined previously following the incremental ramp test. They then conducted a 5-s isokinetic maximal sprint and following 5-min rest undertook the fixed RPE protocol. Upon entering the environmental heat chamber, a standardised 23-min that included the warm-up procedures, rest periods and pre-test sprint, was undertaken before the participants started the fixed RPE trial.

*Isokinetic sprint*

Participants performed a 5-s sprint at maximum effort from a standing start on an ergometer (Lode Excalibur Sport, The Netherlands), with pedalling rate constrained to 70 r/min (isokinetic mode). These efforts were made 5 min prior to and immediately following (within 10-s) the fixed RPE protocol. Instantaneous peak power (W) was recorded as an indicator of fatigue after each trial (Coelho et al. 2015).

*Fixed RPE protocol*

Participants were instructed to cycle at a power output that was perceived to represent an RPE of 16 on the 15-grade Borg scale (Borg 1982) and to adjust their power output such that an RPE of 16 was maintained. An RPE of 16 represents a verbal cue of between 'hard' and 'very hard' on the Borg Scale. The highest average 30-s power output achieved during the first 3-min of the fixed RPE trial was recorded and participants exercised until their power output declined to 70 % of this initial value. The trial was stopped when power output fell below

this value for 2-min. Standardised feedback every ~2-min was given to remind participants to maintain an RPE of 16. Participants were encouraged to constantly reassess whether they were still exercising at RPE-16. They were blinded to distance covered, elapsed time, heart rate, power output.

**Measurements**

*Core & skin temperature*

Rectal (as a core temperature surrogate) and skin temperatures were recorded every 5-min during the experimental trials using a scanning thermometer type CDS 1.0 (Edale Instruments Ltd, Cambridge, UK). Participants inserted a rectal thermometer (Edale Instruments Ltd, Cambridge, UK) 10 cm beyond their anal sphincter to assess core temperature. Skin thermistors (Grant Instruments Ltd., Cambridge, UK) were attached at four locations on the right side of the body: midpoint of the right pectoralis major ($T_{chest}$), midpoint of the triceps brachii lateral head ($T_{arm}$), right rectus femoris ($T_{upperleg}$), and right gastrocnemius lateral head ($T_{lowerleg}$) (Ramanathan 1964). Weighted skin temperature ($T_{skin}$) from four sites was then calculated using the following equation (Ramanathan 1964):

$$T_{skin} = 0.3 \text{ x } (T_{chest} + T_{arm}) + 0.2 \text{ x } (T_{upperleg} + T_{lowerleg})$$

Participants recorded semi-nude body mass (cycling shorts only) prior to entering the heat chamber and immediately following the completion of the experimental trial after wiping off sweat with a towel. No water was ingested during exercise in the heat. Rate of weight loss (in kg/h) was then calculated to provide an indication of sweat loss (Baker et al. 2009).

*Cardiorespiratory measures*

Oxygen consumption ($\dot{V}O_2$), respiratory frequency (R$f$), tidal volume (VT) and minute ventilation (VE) was measured using a telemetric portable gas analyser (CosMed K4b2 Portable, Rome, Italy) which was worn across all trials. The gas analyser was calibrated before every trial with gases of known concentration (16% $O_2$, 5% $CO_2$, BAL. $N_2$) and the turbine volume transducer was calibrated using a 3 L syringe (Hans Rudolph, Kansas City, USA). Heart rate was recorded continuously throughout the trials (Polar Heart Rate Monitor M400, Warwick, UK) that telemetrically emitted the data to the K4b2 portable unit.

*RPE & Thermal sensation/comfort scales*

Participants were thoroughly briefed on the RPE scale before commencing the fixed RPE trials. In line with ACSM guidelines (American College of Sports Medicine 2000), participants were instructed to pay close attention to how difficult the exercise felt, combining total exertion, fatigue, and physical stress in the heat, without considering one particular factor such as leg pain, shortness of breath or anticipation of how they might feel several minutes later. We attempted to anchor the RPE scale by highlighting the self-reported RPE during the early stages of the incremental ramp test (RPE ~10-11) and the final stages of the test (RPE ~19-20). To further enable visualisation of the intensity, participants were provided with associations between the RPE and intensity-duration relationships. An example of this was the guidance that an RPE of-13 was akin to a 2-h cycle,

whilst holding a conversation; RPE-15 being close to a 1-h steady-state maximal effort, where sustained conversation would be difficult; and RPE-16 being a maximal effort they could only sustain for around 25-35 min. In addition, participants where familiarised with the thermal sensation scale and thermal comfort scale. Laminated scales were held in front of the participants during exercise and they were asked to indicate thermal comfort and sensation by pointing to the appropriate point on the scale. Thermal comfort (TC) was recorded on the Bedford 7-point analogue scale where -3 = "much too cool", 0 = "comfortable", and 3 = "much too warm" (Bedford 1936). Thermal sensation (TS) was recorded on an adapted ASHRAE 9-point analogue sensation scale where -4 = "very cold", 0 = "neutral", and 4 = "very hot" (Zhang et al. 2004). Subjective ratings were recorded in 1.0 increments every 5 min during the experimental trials.

*Mouth rinse*

Participants were given 25 ml solution to rinse 1.5 min prior to the main fixed RPE trial and at regular 10-min intervals (therefore delivered at -1:30, 8:30 and 18:30 min). They were instructed to swill around the mouth for 5-s before spitting into a bowl without swallowing. L-Menthol solution was formulated from menthol crystals (House of Flavours, Gloucestershire, UK) dissolved in de-ionised water heated to 40 ºC at a concentration of 0.64 mM (0.01 %). The solution was then stored at 5 ºC for up to 2 months. Prior to use, solutions were aliquoted for mouth swill and warmed to 19.8 ± 0.4 ºC. A placebo mouth rinse was made using an apple flavoured non-calorific artificial sweetener consisting of sucralose (FlavDrops, MyProtein, Norwich, UK) dissolved in 25 ml of deionised water and warmed to 19.7 ± 0.6 ºC.

**Statistical analysis**

All statistical analyses were performed using SPSS (IBM SPSS statistics 22 Inc, USA). A two-way analysis of variance (ANOVA) for repeated measures was used to test for within-group effects across time in both conditions. If sphericity was violated a Greenhouse-Geisser correction was applied. When a significant difference was found for main effect (trial or time), post-hoc pair-wise comparisons were made incorporating a Bonferroni adjustment. Magnitude of effect was calculated with partial eta-squared ($\eta_p^2$) according to the following criteria: 0.02, a small difference; 0.13, a moderate difference; 0.26 a large difference (Cohen 1988). Differing trial durations meant that power data was normalized with respect to time, and for illustration purposes with respect to starting power output. Normalized power output data was plotted from 30-100 % of trial duration using Prism (GraphPad, Inc. version 7.0, USA). The slope values of the regression lines were compared using a repeated-measures analysis of variance and magnitude of effect calculated for the difference in correlations (Cohen's *q*) according to the following criteria: 0.10, a small difference; 0.30, a moderate difference; 0.50 a large difference (Cohen, 1988). Peak sprint power was analyzed by a 2-tailed paired sample *t*-test and magnitude of effect calculated (Cohen's *d*) according to the following criteria: 0.2, a small difference; 0.5, a moderate difference; 0.8 a large difference (Cohen 1988). Data are presented as mean ± SD (*n* = 8). Significance was set at $P < 0.05$.

## Results

### Effect of L-Menthol on exercise performance

All data sets were normally distributed and there was no trial order effect ($P > 0.05$). Trial duration was longer in the L-Menthol condition compared to placebo (23:23 ± 3:36 min and 21:44 ± 2:32 min, respectively) ($t_{(7)} =$ 2.38, $P = 0.049$; $d = -0.53$), representing a ~7 % increase in exercise time (Figure 1). Power output in both conditions decreased with time ($F_{(3,20)} = 60.19$, $P = 0.000$; $\eta_p^2 = 0.464$); however, power output was higher across the L-Menthol condition (L-Menthol: 173 ± 24 W, Placebo: 167 ± 24 W, $F_{(1,7)} = 6.05$, $P = 0.044$; $\eta_p^2 =$ 0.896), despite a similar self-selected starting power output during the first 30 s of exercise (L-Menthol: 186 ± 24 W, Placebo: 186 ± 25 W, $P > 0.05$; $d = 0.01$) (Figure 2A). A linear decrease in power output was noted from 30-100 % of the trial duration in both conditions with correlation coefficients of 0.96 and 0.97 for placebo and L-Menthol, respectively. The rate of decrease in power output was descriptively greater in the L-Menthol condition (L-Menthol: -0.75 ± 0.1 *vs.* placebo: -0.69 ± 0.1 W/% time) although this was not significant ($F_{(1,12)} =$ 0.46, $P = 0.513$, $q = 0.12$) (Figure 2A inset). Isokinetic peak power sprints were decreased by 9.0 % between the pre- and post- L-Menthol trial (1000 ± 196 *vs.* 911 ± 198 W; $t_{(7)} = 3.21$, $P = 0.015$; $d = -0.45$) when compared to a non-significant 3.4 % decrease in the placebo condition (949 ± 207 *vs.* 916 ± 153 W; $t_{(7)} = 1.19$, $P = 0.275$; $d = -0.18$) (Figure 2B).

**Insert figure 1 showing trial duration**

**Insert figure 2(A/B) %power as %time & bar chart showing sprints **

### Warm up RPE-16 ramp test

During the pre-experimental self-selected ramp to an RPE of 16, final power output was not significantly different across the three trials ($P > 0.05$) in the hot environment (34.8 ± 1.0 ºC) (trials comprised the familiarisation, menthol and placebo sessions) (Table 1).

** Insert table 1 displaying power data **

### Thermoregulation

Thermal sensation scores significantly increased with time ($F_{(1.76,12.31)} = 59.27$, $P < 0.001$; $\eta_p^2 = 0.894$); however, thermal sensation scores were lower across the L-Menthol condition ($F_{(1,7)} = 6.73$, $P = 0.036$; $\eta_p^2 =$ 0.490) (Figure 3A). In contrast, whilst thermal comfort scores increased with time ($F_{(1.75,12.28)} = 44.74$, $P <$ 0.001; $\eta_p^2 = 0.865$), there was no difference between conditions ($F_{(1,7)} = 1.759$, $P > 0.05$; $\eta_p^2 = 0.201$) (Figure 3B). Core temperature after the standardized warm-up was not different at 37.5 ± 0.4 ºC and 37.6 ± 0.6 ºC for L-Menthol and placebo, respectively ($P > 0.05$). Core temperature increased with time in both conditions ($F_{(4,28)} =$ 46.46, $P < 0.001$; $\eta_p^2 = 0.869$) but with no difference between condition (Figure 4A). Mean skin temperature was not different after the standardized warm-up at 35.7 ± 0.4 ºC and 36.0 ± 0.7 ºC for menthol and placebo,

respectively. Skin temperature also increased with time in both conditions ($F_{(4,28)}$ = 72.195, $P < 0.001$; $\eta_p^2$ = 0.912) with no difference between conditions (Figure 4B). Body mass was lower pre and post-test ($P < 0.001$) in the heat chamber; however, there was no difference between condition both at baseline and post-test. Rate of body mass loss was $1.1 \pm 0.3$ (kg/h) and $1.2 \pm 0.6$ (kg/h) for menthol and placebo respectively (data not shown).

**Insert fig 3A/B) graphs showing comfort/sensation **

**Insert fig 4 (A/B) graphs showing core/skin temp **

**Cardiorespiratory measures**

All cardiorespiratory variables measured increased with time across both conditions ($P < 0.001$). However, there was no significant difference between conditions, oxygen consumption ($\dot{V}O_2$) ($F_{(1,5)}$ = 3.383, $P > 0.05$, $\eta_p^2$ = 0.404), respiratory frequency (R$f$) ($F_{(1,7)}$ = 2.738, $P > 0.05$, $\eta_p^2$ = 0.281), tidal volume (VT) ($F_{(1,7)}$ = 0.123, $P > 0.05$, $\eta_p^2$ = 0.017), minute ventilation (VE) ($F_{(1,7)}$ = 1.561, $P > 0.05$, $\eta_p^2$ = 0.182),  and heart rate (HR) ($F_{(1,6)}$ = 0.834, $P > 0.05$, $\eta_p^2$ = 0.122),  (Figure 5 A-D).

**Insert fig 5 (A/B/C/D) graph RF / TV /  HR / VO2 **

**Discussion**

Our key findings were that oral application of a non-thermal cooling L-Menthol mouth rinse increased exercise duration by ~ 7 % in the heat during a self-regulated fixed RPE trial. Power output during the L-Menthol trial was also significantly higher, suggesting that participants had adopted a greater initial work rate in the heat. This reflects a change in the pacing strategy of the participants in the L-Menthol condition. Whilst non-significant, there was also evidence of an accelerated linear decrease (small difference) in power output after the first 30 % of the trial was completed as a result of the higher work rate adopted in the menthol trial. In addition, a post-test isokinetic sprint revealed a greater decrement (small to moderate difference) in peak power in the L-Menthol compared to placebo condition (9.0 % *vs*. 3.4 %, respectively). Together, this would suggest that although workload was higher in the menthol condition, the capacity for generating peak power after the trial was reduced, indicating that the participants worked harder and would have accumulated greater levels of peripheral fatigue. Key to these observations is that L-Menthol significantly reduced thermal sensation, which may explain the increase in power output observed at the beginning of the trial, and the subsequent accelerated decline in performance and measurable difference in peak power pre- and post-test. All of these changes occurred without any significant difference between conditions in core or skin temperature.

In the heat, participants were asked to set their workload corresponding to a perceived exertion of 16 on the RPE scale prior to the main experimental trial. The selected power output was the same across the three trials in the heat, suggesting that the participants' initial selection, and presumably planned strategy, of power output was replicable and did not differ prior to administration of the mouth wash. This is in line with previous observations suggesting that initial power output is set on a feed-forward manner, based on expectations of exercise (Tucker et al. 2006; Tucker 2009). Following oral rinsing of L-Menthol, power output at the beginning of the fixed RPE trial was similar for the first 30-s of exercise. However, power output subsequently rose by the end of the first minute and remained significantly higher across the L-Menthol trial. Therefore, participants voluntarily adopted a higher work rate, after rinsing with L-Menthol mouth rinse in the heat. Interestingly, following administration of L-Menthol, participants experienced an accelerated decrease in power output (small effect) after ~ 30 % of trial completion despite power output remaining elevated. This could suggest that L-Menthol plays a greater role, initially, thereafter diminishing as a function of time. This could relate to a deprioritising of afferent cues from the oral cavity when homoeostasis is challenged through core and skin temperature increases, thus generating stronger afferent feedback. Indeed, it has been suggested that acute threats to thermal homeostasis are prioritised, such that they override the ergogenic effects of external cueing, such as deceptive feedback (Waldron et al. 2014) and nullify the effects of mental fatigue (Van Cutsem et al. 2017).

Previous research has demonstrated an improvement in endurance performance following periodic mouth rinsing with L-Menthol in the heat (Mündel and Jones 2010). Here, they postulated this may have been linked to a reduced sense of effort. Adopting a different approach, thermal perception was modulated by thermal and non-thermal face cooling during a similar fixed RPE protocol (Schlader et al. 2011b). The authors reported changes in thermoregulatory behaviour as a result of modified thermal perception, which translated into longer exercise duration. In addition, another study has reported a change in thermal sensation and improved running

performance after administration of an L-Menthol mouth rinse in contrast to no effect on performance or thermal sensation with prior ingestion of an ice slurry which reduced core temperature (Stevens et al. 2015). Together, thermal sensation appears to be an important driver of thermoregulatory behavior and the evidence suggests that non-thermal cooling could be a relatively novel strategy to improve heat tolerance and facilitate exercise capacity in the heat. In this study, we have demonstrated the direct effect of oral rinsing with a non-thermal cooling strategy on subjective pacing at a fixed perceived intensity. We can also directly report that administration of L-Menthol modulates the work rate across the trial facilitating a greater exercise duration in the heat.

Thermal comfort reports a subjective opinion on the thermal environment (The Comission for Thermal Physiology of the IUPS 2001) and was shown to increase over time but was not different between L-Menthol and placebo conditions. Meanwhile perception of thermal sensation, which assesses the relative intensity of temperature being sensed (Gagge et al. 1967), was made cooler across the L-Menthol condition. Therefore, participants began the exercise trial perceiving their thermal sensation to be measurably cooler in the L-Menthol condition reporting that they felt "slightly warm" versus "warm" in the placebo condition. This distinction in thermal sensation was apparent throughout the trial between conditions although evidently narrowed towards the end when perhaps the intervention becomes less effective. A cooler thermal sensation was also evidenced by the higher work rate adopted early in the L-Menthol exercise trial which may have facilitated the reduction in perceived effort for a fixed work rate. Perception of effort has been described by two models: as a conscious integration of afferent information from peripheral receptors (Hampson et al. 2001; Noakes 2004; Tucker 2009) or alternatively, it has been attributed to conscious awareness of central motor command to the working muscles (Poulet and Hedwig 2007; Marcora et al. 2008; Marcora 2009; de Morree et al. 2012). Mechanistically, L-Menthol-induced cold sensation is thought to primarily rely on sensitization of the TRPM8 voltage-gated ion channel present on Aδ and C- sensory nerve fibres (McKemy et al. 2002; Peier et al. 2002; Andersen et al. 2014), although other channels such as TREK-1/TRAAK have been proposed (Noel et al. 2009). Centrally, these neurons synapse with interneurons, relaying information to the thalamus and then to the cortex, where subjective interpretation of the stimulus occurs, leading to perception (de León-Casasola 2009; Andersen et al. 2014; Haggard and de Boer 2014). Therefore, it seems plausible that menthol elicits an afferent cue, capable of subsequent integration into a central regulator that resets exercise intensity.

The oral cavity is one of the most densely innervated parts of the body in terms of peripheral receptors (Haggard and de Boer 2014). It is therefore interesting to speculate on how stimulation of such a densely innervated region may relay afferent signals to the brain. Research examining topical application of menthol to the body, appears to lower thermal sensation but does not translate to a measureable effect on performance (Barwood et al. 2012). It is feasible that thermal receptors in the oral cavity provide a more potent target for non-thermal cooling than that the more sparsely innervated regions of the body. If this is the case, the magnitude of afferent feedback from the oral cavity could, logically, be prioritised by a central regulator. Future research should try to understand the interplay between different afferent stimuli, such as that discussed herein, and their central integration in driving thermoregulatory behaviour. It is important to note that menthol application to the skin has been shown to impair the sweating response and cause vasoconstriction (Kounalakis et al. 2010), leading to an increase in core temperature (Gillis et al. 2010). This would potentially negate any improvements in

performance from lowering thermal sensation as the central regulator is thought to integrate afferent information from various sources, including the skin. In contrast, topical application of a menthol cream to the face, a smaller surface area which did not affect sweat rates, did lead to increased work output (Schlader et al. 2011b), although cooling of the face has been shown to be much more effective in supressing thermoregulatory behaviour and thermal discomfort than other parts of the body (Cotter and Taylor 2005).

The physiological responses to exercise in the heat have been well described. Steady state exercise induces a linear increase in core temperature, skin temperature, heart rate and $\dot{V}O_2$ (Galloway and Maughan 1997; González-Alonso and Calbet 2003). In this study, all of the physiological responses were characteristic of that described in high ambient temperatures as a function of exercise time. There were no differences between conditions, despite the significant differences in thermal sensation and power output. Although not significantly different, $\dot{V}O_2$ was descriptively higher in the L-Menthol condition and represented by a large effect size suggesting it may be of practical significance. Presumably this can be attributed to the adopted exercise strategy, whereby a higher power output was adopted earlier in the L-Menthol condition. Increases in minute ventilation have previously been described after mouth rinsing with L-Menthol whilst exercising in the heat (Mündel and Jones 2010; Stevens et al. 2015). Indeed increases in respiratory frequency and minute volume have been directly linked to perceived exertion (Noble et al. 1973). However, in this study, there were no reported changes in tidal volume or respiratory frequency (figure 5), the determinants of minute ventilation. Much of the research examining L-Menthol on respiratory function is based on animal models, were a reduction in ventilation has been reported (Orani et al. 1991; Sant'Ambrogio et al. 1992; Curran et al. 1998). Studies in humans at rest have also reported that L-Menthol elicits no changes in ventilation (Nishino et al. 1997; Pereira et al. 2013). This suggests that any adjustment in the perceived effort associated with the self-selected exercise intensity during the L-Menthol trial, was not linked to changes in respiratory control. The disparity in findings may relate to the nature of exercise, namely sub-maximal self-paced rather that maximal efforts, but this remains to be elucidated.

The findings from our present study increase our understanding of non-thermal cooling and the impact on pacing and exercise duration in the heat. Nevertheless, we acknowledge that there may be limitations with our findings. The fixed RPE protocol used in this study has not been extensively tested for reliability with respect to duration and this remains to be explored. Thermal comfort and thermal sensation scales that are currently used in the literature may require greater scrutiny and validation as described (Schweiker et al. 2016). In addition, blinding participants to the cooling sensation induced by L-Menthol is difficult and so we chose to use a bitter tasting placebo solution to equally stimulate the oral cavity due to the difficulty replicating the taste of menthol without eliciting a cooling effect.

We suggest that future research is directed towards understanding the mechanisms through which oral administration of L-Menthol elicits changes in thermal sensation and RPE. The role of L-Menthol in modulating arousal or motivational levels could be considered part of the mechanistic process as there are commonalities between our results and that of other studies. For example, administration of a drug that modulates arousal, motivation and reward in the brain (Watson et al. 2005; Roelands et al. 2012; Cordery et al. 2016) has previously improved time-trial performance in the heat, despite a higher core temperature. Interestingly, in

contrast to the current study, perception of effort and thermal stress remained the same as reported in the placebo trial, suggesting that motivation or the drive to exercise was enhanced. It was suggested that this may be due to overriding inhibitory signals from the central nervous system that result in cessation of exercise due to hyperthermia (Zheng and Hasegawa 2016), hence removing a "thermoregulatory brake". Similar mechanisms may underlie application of oral L-Menthol, whereby modulation of neurotransmitters increase reward and motivational pathways. Future research should seek to establish brain regions activated by L-Menthol in temperate and hot conditions and how this may progress when heat stress is heightened during exercise in hot conditions. Caution must also be taken when administering L-Menthol to athletes exercising in the heat, due to the potential danger of thermal mis-regulation and the subsequent development of harmful hyperthermia.

In summary, a non-thermal cooling L-Menthol mouth rinse lowered thermal sensation, which reduced perceived effort, resulting in an altered pacing strategy, elevated power output and extended exercise time in the heat at a fixed RPE. Together, this suggests that L-Menthol can override thermal homeostasis to enable achievement of a higher workload.

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**Table 1** Final power output (W) during a self-determined ramp protocol. Resistance on an ergometer was modified by the participant to equate to a perceived RPE of 16 in exercise trials in the heat (34.8 ± 1.0 ℃) presented in order of trial. Mean ± SD (n = 8)

|                 | Trial 1   | Trial 2   | Trial 3   |
| --------------- | --------- | --------- | --------- |
| Final Power (W) | 200 ± 28  | 195 ± 30  | 196 ± 32  |

**Figures**
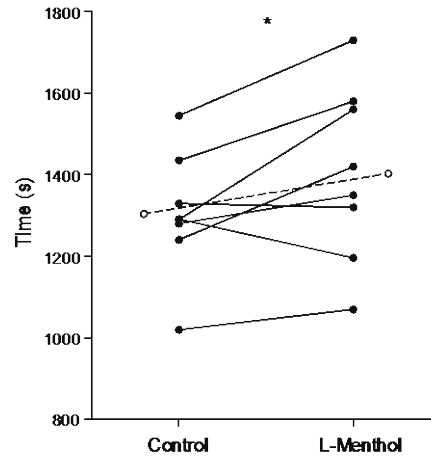


**Fig 1** Individual and mean trial duration times for L-Menthol and placebo. Dotted line indicates average time. * denotes significance difference (P < 0.05)
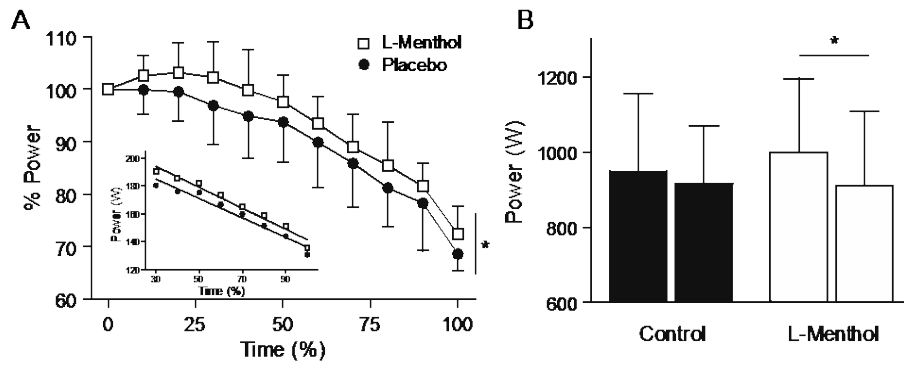
**Fig 2** (A) For illustration purposes, power output expressed relative to the first 30 s of exercise and plotted against trial duration expressed as a percentage of final time for L-Menthol (white square) and placebo (black circle). Inset displays absolute mean power output data from 30-100 % of trial duration fitted with a line of best fit. (B) Isokinetic (70 rpm) 5 s peak power sprints pre and post-trial for L-Menthol (white bars) and placebo (black bars). All data are shown as mean ± SD, ($n$ = 8). * denotes significant difference (P < 0.05).
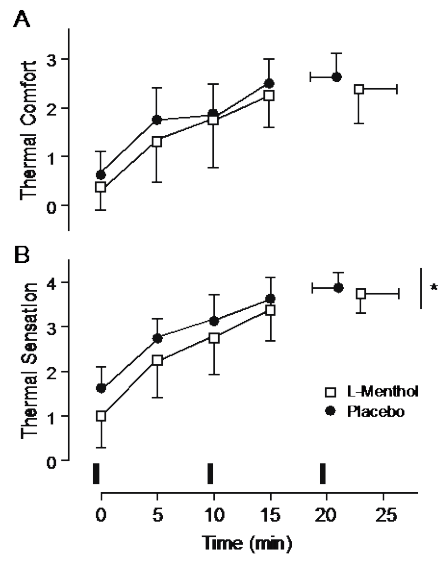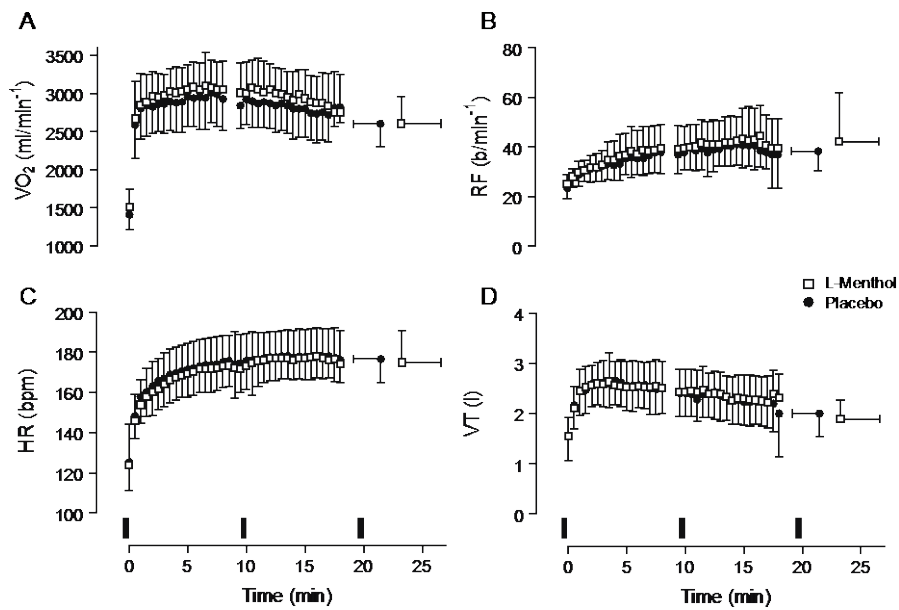
**Fig 3** (A). Thermal comfort scores and (B). thermal sensation scores for L-Menthol (white square) and placebo (black circle) conditions. Black boxes on the horizontal axis indicate application of mouth rinse (5 s). All data are shown as mean $\pm$ SD, ($n = 8$). * denotes significant difference (P < 0.05).
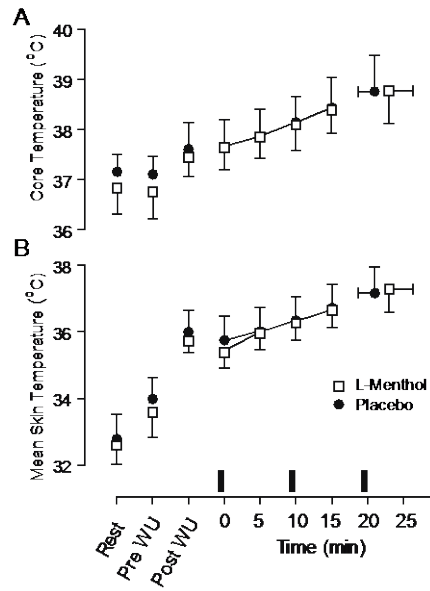
**Fig 4** (A). Rectal temperature ($^{o}$C) and (B) mean skin temperature ($^{o}$C) for L-Menthol (white square) and placebo (black circle) conditions. Black boxes on the horizontal axis indicate application of mouth rinse (5 s). All data are shown as mean $\pm$ SD, ($n = 8$).

**Fig 5** Absolute data displayed in 30 s epochs over the first 18 min of exercise and end value for (A). oxygen consumption (ml/min), (B). respiratory frequency (b/min[-1]), (C). heart rate (b/min) and, (D) tidal volume (l) for L-Menthol (white square) and placebo (black circle) conditions. The gap in data represents removal of the facemask to swill with mouth rinse at 8:30 and then 18:30 min. Black boxes on the horizontal axis indicate application of mouth rinse (5 s). All data are shown as mean ± SD, ($n$ = 8).