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Infection as an Exertional Heat Illness Risk Factor: A Prospective Cohort Study

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ABSTRACT

Purpose: Strenuous physical activity for work or leisure increases the risk of exertional heat illness (EHI), which can be fatal. Respiratory infection may increase EHI risk, but empirical evidence is equivocal and relies upon clinical case reviews that lack objective measures and comparator controls. This prospective cohort study investigated the association between respiratory infection and EHI. **Methods**: N=807 UK infantry recruits (M=805/F=2) completed a 6.4-mile loaded march between Spring and Fall (2021-2024, WBGT, 11.2 ± 3.6°C). Participants completed the Jackson Common Cold Questionnaire on each of the 3 days preceding and before the loaded march on Day 0. Additional measures included clinical pathology on throat swabs (Day -3 and -1), serum C-reactive protein (CRP; Day -1) and gastrointestinal temperature (T_{gi}, Day 0). EHI was classified as mild (exercise-induced headache, dizziness, or nausea) or severe (CNS disturbance plus hyperthermia and/or end-organ damage). Logistic regression examined the association between respiratory infection and EHI after full adjustment for widely considered EHI risk factors. **Results**: N=118 participants were classified as mild (15%) and N=40 as severe EHI (5%). The likelihood of severe EHI was increased four-fold with respiratory infection symptoms on Day -1 and 0 (OR=4.09, 95% CI=1.29–12.90, *P*=0.016) and three-fold when restricting analysis to symptoms on Day 0 (OR=2.83, 95% CI=1.02–7.86, *P*=0.046). Participants with respiratory infection symptoms exhibited increased pathogen expression, systemic inflammation (CRP >3 $mg \cdot L^{-1}$) and pre-loaded march T_{gi} (+0.3°C, *P*=0.023). Respiratory infection symptoms were not associated with mild EHI susceptibility. **Conclusions**: Ongoing respiratory infection was associated with an increased likelihood of severe exertional heat illness. Individuals at risk of exertional heat illness (e.g., athletes) should avoid strenuous physical

activity when suffering respiratory infection symptoms. **Key Words:** HEAT INJURY, HEAT STRESS, HEATSTROKE, RESPIRATORY INFECTION

INTRODUCTION

The anticipated rise in global temperature in the 21st Century will likely increase the risk of heat illness, which in its severest form can be fatal (1). Accordingly, there is a growing need to advance current knowledge of heat illness etiology and to develop mitigation strategies to reduce heat illness prevalence. Heat illness is commonly classified as either classical or exertional (EHI). Classical heat illness predominantly occurs in older individuals, who often have comorbidities, during passive exposure to hot environmental conditions (2). EHI typically occurs in young and seemingly healthy individuals (e.g., military personnel and athletes) during strenuous physical activity in both cool and hot environmental conditions (3, 4). EHI is considered to occur on a severity spectrum from mild (i.e., heat exhaustion) to severe (i.e., heat stroke). Common signs and symptoms of mild EHI include headache, nausea and dizziness (5). Central nervous system disturbance is the defining feature of severe EHI, typically accompanied by hyperthermia and evidence of end-organ damage in the days following the episode (3). Widely reported risk factors for EHI include low aerobic fitness, an elevated wet bulb globe temperature (WBGT), hypohydration and high motivation (5). Unfortunately, much of the underpinning evidence outlining EHI risk factors is derived from retrospective clinical case reviews, which lack objective measures and comparator controls (6-9). Furthermore, widely reported risk factors for EHI are absent in many cases, pointing to the involvement of alternative risk factors in the development of a significant number of EHI cases (7, 8).

Expert statements highlight ongoing infection as a likely predisposing EHI risk factor, but empirical evidence in humans is equivocal (3, 5). Experimental evidence examining the pathogenesis of EHI in rodents supports the proposition that infection and associated inflammation increase EHI risk (10-12). For example, exogenous administration of viral or

bacterial mimics, or an inflammatory stimulant during heat stress can increase deep body temperature and elevate both the likelihood and severity of heat stroke in rodents (10-12). In humans, a case study of an individual suffering from a bacterial infection showed increased heat strain both at rest and during exercise-heat-stress (13). Other case studies have proposed that recent infection was a contributing factor for exertional heat stroke in a single well-trained runner during a marathon (14) and in three of six EHI fatalities in Israeli Defense Forces (7). However, clinical reviews of military EHI cases present a mixed picture regarding a role for recent or ongoing infection in EHI etiology. One examination of US military clinical records showed that respiratory infection in the preceding week increased the risk of both mild and severe EHI (15). Whereas other analyses of US and UK military clinical records conclude that 'prior illness' or 'intercurrent febrile or infectious illness' did not increase severe EHI risk (8, 9). Unfortunately, these clinical case reviews are limited by a lack of objective measures (e.g., for respiratory infection and EHI) and comparator controls; individuals who complete the same exercise but do not experience EHI. As such, a conclusion about the influence of respiratory infection on EHI susceptibility cannot be reached until prospective cohort studies are completed that include the requisite controls, objective assessments for both respiratory infection and EHI and statistical analyses that account for other widely considered EHI risk factors.

The aim of this prospective cohort study was to examine the association between respiratory infection and EHI in military recruits undertaking strenuous physical activity. It was hypothesized that respiratory infection would be associated with increased EHI susceptibility.

METHODS

Ethical approval

The data presented here were collected as part of a prospective cohort study investigating risk factors for EHI. This study received ethical approval from the UK Ministry of Defence Research Ethics Committee (2029/MODREC/21), was registered at www.clinicaltrials.gov (NCT04979455) and conducted in accordance with the Declaration of Helsinki (2013).

Participants

Between Spring and Fall (2021–2024), N = 978 infantry recruits at the Commando Training Centre Royal Marines, Lympstone, UK were briefed and assessed for eligibility. A total of N = 807 recruits (M=805/F=2; mean ± SD, age 22 ± 3 years; height 179.6 ± 6.1 cm; body mass 80.7 ± 7.6 kg) provided written informed consent to participate in the study and completed data collection (Figure 1). Eligible participants were 17–35 years old, free from cardiovascular, respiratory (e.g., asthma), digestive, kidney, neurological or endocrine disorders, were in week 22 of Royal Marine Commando Training or week 7 of the All Arms Commando Course and scheduled to complete a criterion 6.4-mile loaded march.

Experimental procedures

To prospectively examine the association between respiratory infection and EHI, respiratory infection symptoms were recorded using the Jackson Common Cold Questionnaire (16), alongside other widely considered EHI risk factors, in the three days preceding (Day -3 to Day -1) and before exercise on the day of the 6.4-mile loaded march (Day 0; Figure 2). In addition, throat swabs were collected to identify the presence of respiratory pathogens (Day -3 and Day -1) and serum C-reactive protein (CRP) was measured on Day -1 to provide a measure of systemic inflammation. At 2100 hours on Day -1, participants were given an ActiGraph

(ActiGraph GT3X, Ametris, Pensacola, USA) to wear on their non-dominant wrist to assess physical activity and swallowed a telemetry capsule to assess gastrointestinal temperature (T_{gi}) during the loaded march.

Height and body mass were measured to determine body mass index (BMI). Training records were accessed to provide a measure of aerobic fitness using a 2.5-mile maximal fitness test performed ~9 days before the loaded march; medical records were accessed to determine physician diagnosed illness and whether medications had been prescribed in the 28 days preceding the loaded march and participants completed questionnaires assessing previous EHI symptoms ($\leq$ 2 years); heat-acclimatization status (i.e., regular sauna or hot bath user and/or travel to a hot climate within the last month) and motivation to successfully complete the loaded march (17).

Upon awakening on Day 0, participants provided a urine sample to determine hydration status. Participants then completed questionnaires asking whether they had taken any over-the-counter medications (e.g., acetaminophen, antihistamine etc.) or were currently experiencing seasonal allergic rhinitis (hay fever) symptoms, or symptoms commonly associated with mild EHI e.g., headache, nausea and dizziness (5). Accounting for the presence of seasonal allergic rhinitis symptoms increases our confidence that respiratory symptoms assessed using the Jackson Common Cold Questionnaire were likely of infectious origin (18). Moreover, by assessing headache, nausea and dizziness symptoms at rest we were able to subsequently isolate exercise-induced mild EHI symptoms during the loaded march. At ~0700 hours, WBGT was recorded at the location for the start and finish of the loaded march (QUESTemp 34, Quest Technologies Ltd, London, UK). Following a standardized warm-up led by the training staff, participants commenced the loaded march. Participants wore standard issue long-sleeved T-shirt, combat

trousers and boots, and carried an external load and rifle totaling ~14.5 kg. The loaded march was completed on a standardized undulating road route and, in line with local policy, a 1–2 minute ad libitum water stop was provided after ~30 minutes. Participants marched or ran as a unit at ~10 minute mile pace, as directed by the training staff and completed the 6.4-mile loaded march in 66 ± 2 minutes. Upon cessation of exercise, each participant met with a member of the research team to assess exercise-induced symptoms of mild EHI and to complete the Quick Confusion Scale (QCS) (19). The validated QCS assesses orientation, memory and concentration providing objective evidence of CNS disturbance, the main discriminatory feature of severe EHI (3, 5). In participants who sustained an episode of EHI, where available, primary care medical records were accessed to provide measures of liver and kidney damage in routine serial blood tests (Day 0 to Day +3) (5).

Experimental measures

Respiratory infection. Respiratory infection symptoms were assessed using the Jackson Common Cold Questionnaire which assesses the severity of eight clinical symptoms (headache, sneezing, chilliness, sore throat, nasal discharge, nasal obstruction, cough and malaise) and was developed following the inoculation of > 1,000 individuals by nasal instillation of common cold secretions (16). Each clinical symptom is scored on a 4-point scale; whereby, 0 = no symptom, 1 = mild symptom, 2 = moderate symptom and 3 = severe symptom. A daily symptom score ≥ 6, equivalent to three moderate symptoms, was used to determine a respiratory infection on two consecutive days (e.g., Day -1 and Day 0) (20, 21). From a practical implementation perspective, as respiratory symptoms could be assessed pre-exercise as a health pre-screen, we also report respiratory infection as a symptom score ≥ 6 on Day 0. Respiratory pathogen carriage was assessed using standard procedures at Public Health Wales (Wales Specialist Virology Centre).

Briefly, trained research staff wiped a cotton swab twice on each side of the participant's tonsils. Respiratory swab samples were later analyzed using Polymerase Chain Reaction analysis (Allplex™ Respiratory Panel Assays, INC., Seoul, Korea) (22). Pathogen assessment included acute respiratory illness causing targets e.g., influenza A H1 and H3, respiratory syncytial virus A, parainfluenza types 1 to 4, human metapneumovirus, rhinovirus, human coronaviruses OC43, 229E and NL63 and SARS-CoV-2. To assess serum CRP, a marker of systemic inflammation, a blood sample was collected on Day-1 by venipuncture from an antecubital vein into a plain 6 mL vacutainer tube (Becton Dickinson, Oxford, UK). Samples were left to clot for 1 hour at room temperature and then centrifuged for 10 minutes (1500 *g*, 4 °C). Serum was aliquoted, frozen and stored at -80 °C. Thawed serum samples were later analyzed for CRP using an immunoturbidimetric assay (Tina-quant C-Reactive Protein IV kit; intra-assay CV 5.5%) on a clinical chemistry analyzer (Cobas 701 analyzer, Roche Diagnostics, IN, USA). Literature defined clinical thresholds classified serum CRP as low (< 1 $mg \cdot L^{-1}$) or high (> 3 $mg \cdot L^{-1}$) (23, 24).

Urine hydration status. On Day 0 participants provided an awakening urine sample in a 25 mL universal tube and urine osmolality was assessed using freezing point depression (Gonotec Osmomat 3000 basic, Gonotec, Berlin, Germany). Urine samples were analyzed in duplicate, but if the values from the two measurements differed by greater than ± 2 $mOsmol \cdot kg^{-1}$ between 0–400 $mOsmol \cdot kg^{-1}$, or greater than ± 4 $mOsmol \cdot kg^{-1}$ when urine osmolality was > 400 $mOsmol \cdot kg^{-1}$, replicates were reanalyzed until two consecutive measurements were within the acceptable error margin, in line with manufacturer instructions and local standard operating procedures (25). Literature defined thresholds identified participants as hydrated (< 500 $mOsmol \cdot kg^{-1}$ (26)) or hypohydrated (> 900 $mOsmol \cdot kg^{-1}$ (27)).

Motivation. The Success Motivation questionnaire assessed participants' motivation to successfully complete the 6.4-mile loaded march (17). The loaded march was a criterion test that recruits must pass to progress through military training. The Success Motivation questionnaire consists of 7-items which are rated on a five-point Likert scale (range from 0 'not at all' to 4 'extremely').

Gastrointestinal temperature. T_{gi} provided a measure of deep body temperature during the loaded march. To ensure the error of each validated and CE marked ingestible telemetry capsule was within an acceptable range (± 0.1 °C) (28, 29), prior to ingestion each capsule was submerged in a stirred water bath (SLS Lab Pro Stirred Water Bath SLS1170, Scientific Laboratory Supplies, Nottingham, UK) adjacent to a certified and calibrated thermometer (Spirit ASTM, Cumbria, UK). A correction equation over the biological range (36 °C, 39 °C and 42 °C) was created for each capsule, as previously described (30). Participants ingested a telemetry capsule (CorTemp; HQ Inc., Palmetto, FL, USA [N = 690] or e-Celsius; BodyCap, Caen, France [N = 117]) at 2100 hours on Day -1, allowing ~10 hours for the capsule to transit into the gut and provide a valid T_{gi} during the loaded march on Day 0 (31). Following cessation of the loaded march T_{gi} data was downloaded using a data recorder (HQ Inc., Palmetto, FL, USA or e-Celsius; BodyCap, Caen, France).

Participant classification. Participants were classified as mild or severe EHI using key discriminatory features outlined in expert statements (3, 5, 32). Mild EHI reported exercise-induced symptoms of dizziness, nausea or headache during the loaded march (5, 33). Severe EHI exhibited: 1) CNS disturbance, the main diagnostic criteria for exertional heat stroke, determined as incapacitation (e.g., loss of consciousness) or QCS score ≤ 11 (19) and 2) hyperthermia determined as peak $T_{gi} \geq 39.5$ °C (34), and/or where referred for serial blood testing, evidence of

end-organ damage (Day 0 to Day +3). Acute kidney damage was determined as circulating creatinine ≥ 115 μmol·L^{-1} (35, 36) and acute liver damage as circulating aminotransferase ≥ 89.5 U/L (37, 38). The remaining participants were classified as non-EHI.

Data analyses

All analyses were conducted using SPSS 29.0 (IBM, Armonk, NY, USA) with statistical significance set at $P < 0.05$. Of the N = 807 who completed data collection, N = 805 were male and only N = 2 were female (Figure 1). This was due to the small number of females entering Royal Marine Commando training. In the N = 790 included in data analyses, a small amount of data were missing at random (4%). As small amounts of missing data can lead to bias and reduced statistical power (39, 40) multiple imputation was performed on the full data set using predictive mean matching (50 iterations and 40 imputed datasets) (39, 41). Statistical analysis outcomes from each of the 40 imputed data sets were pooled to account for between and within imputation variations (40). Demographic and infection data were similar between pre and post multiple imputation datasets (Supplemental Table 1, Supplemental Digital Content, http://links.lww.com/MSS/D405).

Data are presented as mean ± SD for continuous variables or absolute numbers and percentages for categorical variables. To account for the influence of variable weather conditions on 2.5-mile aerobic fitness test performance, individual performance times were ranked and tertiled within each troop (low, moderate and high aerobic fitness groups) and treated as categorical data. Motivation data were also ranked and divided into tertiles to identify low, moderate and high categorical groups. Participants were considered as overweight if BMI ≥ 25.0 kg·m^{-2} (42). Actigraphy data were collected at a sampling rate of 30 Hz aggregated into 1-minute epochs. Data were downloaded using ActiLife software (Version 6, Ametris, Pensacola, USA)

and analyzed using the Swartz algorithm to estimate physical activity (step count) from awakening to the start of the loaded march on Day 0 (43). Comparisons between participants identified as non-EHI, mild EHI and severe EHI were assessed using either independent samples *t*-tests or Chi-square, where appropriate. Fully adjusted multiple logistic regression was used to examine the association between respiratory infection and mild EHI or severe EHI, with 'healthy' participants as the reference group. Fully adjusted regression models included aerobic fitness, duration of the loaded march, WBGT, BMI, hydration status, previous EHI symptoms, heat acclimatization status, motivation, prescribed or over-the-counter medication use and hay fever as covariates. Diagnostic checks indicated negligible correlations between respiratory infection and each covariate and among covariates ($r < 0.01$) (44), and minimal multicollinearity (mean variance inflation factor = 1.03, maximum variation inflation factor = 1.06) (45), indicating that each covariate contributed independent information to regression models.

RESULTS

EHI classification

Of the N = 790 participants who completed data collection and were included in analysis, N = 632 were classified as non-EHI (80%), N = 118 as mild EHI (15%) and N = 40 as severe EHI (5%). In addition to presenting with CNS disturbance, severe EHI were hyperthermic (98%) and, where serial blood samples were available exhibited evidence of end-organ damage after the loaded march (Day 0 to Day +3, 100%). The incidence of mild and severe EHI was similar across Spring, Summer and Fall ($\square^2$, $P > 0.050$). Demographic and anthropometric measures were similar between participants classified as non-EHI and either mild or severe EHI ($P > 0.050$, Table 1). Despite all 29 loaded marches being completed in cool environmental conditions (WBGT, 11.2 ± 3.6 °C), WBGT was higher for severe EHI ($P = 0.001$, Table 1) and tended to be

higher for mild EHI compared to non-EHI ($P = 0.076$, Table 1). Those with mild EHI took longer to complete the 2.5-mile fitness test ($P = 0.001$), indicating lower aerobic fitness, and a greater proportion of mild EHI cases reported previous EHI symptoms, compared to non-EHI ($\square^2$, $P < 0.001$, Table 1). Those with severe EHI also tended to take longer to complete the 2.5-mile fitness test and to report previous EHI symptoms compared to non-EHI, but these differences did not reach statistical significance ($P > 0.050$, Table 1). There were no significant differences between non-EHI and either mild or severe EHI for BMI, heat acclimatization status, pre-exercise hydration, medication use or motivation ($P > 0.050$, Table 1).

Respiratory infection and EHI susceptibility

A distinct seasonal pattern of respiratory infection was observed. The frequency of respiratory infections recorded using the Jackson questionnaire was 5% in Spring, 3% in Summer and 9% in Fall ($\square^2$, $P < 0.001$ Fall *vs.* Summer, Day -1 and Day 0). Respiratory infections were recorded in N = 78 participants on Day -3 and Day -2 (10%), in N = 40 on Day -1 and Day 0 (5%) and N = 69 on Day 0 (9%). Accessing medical records showed that only a small number of participants reported to the medical center and were diagnosed with an illness by a physician in the 28 days before the loaded march (Table 1). Ongoing respiratory infection symptoms, assessed using the Jackson questionnaire, were associated with an increased likelihood of severe EHI (Figure 3 and Table 2). Logistic regression, fully adjusted for widely considered EHI risk factors, showed that respiratory infection symptoms on both Day -1 and Day 0 were associated with a 4-fold increased likelihood of severe EHI ($P = 0.016$). Respiratory infection symptoms on Day 0 were associated with a ~3-fold increased likelihood of severe EHI ($P = 0.046$). However, the likelihood of severe EHI was neither increased in participants reporting respiratory infection symptoms on Day -3 and Day -2 ($P = 0.703$, Figure 3 and Table

2) nor in those who were symptomatic on Day -3 and Day -2 but subsequently categorized as healthy by Day 0 (fully adjusted OR = 0.69, 95% CI 0.08–5.83, $P = 0.731$). Respiratory infection symptoms recorded during the three-day monitoring period were not associated with an increased likelihood of mild EHI ($P > 0.050$, Table 2).

Respiratory infection symptoms on both Day -1 and Day 0 increased the expression of common cold causing respiratory pathogens ($\square^2$ $P < 0.001$), the prevalence of systemic inflammation (high CRP >3 $mg \cdot L^{-1}$, $\square^2$ $P < 0.001$) and raised pre-loaded march T_{gi} (Figure 4). After a standardized warmup, pre-loaded march T_{gi} was higher in participants suffering respiratory infection symptoms with accompanying systemic inflammation compared with healthy participants ($P = 0.023$, Figure 4C). This observation occurred despite comparable findings for variables likely to influence exercising T_{gi} including aerobic fitness, body surface area:mass ratio, pre-exercise physical activity (step count from awakening to the start of the loaded march), pre-exercise hydration status and WBGT ($P > 0.050$ RTI *vs*. healthy for all comparisons, Supplemental Table 2, Supplemental Digital Content, http://links.lww.com/MSS/D405).

DISCUSSION

The study aim was to investigate the association between respiratory infection and EHI susceptibility, for the first time using a prospective cohort design that included comparator controls and objective assessments for respiratory infection and EHI. In support of our hypothesis, respiratory infection symptoms recorded the day before and the day of the loaded march were associated with a four-fold increased odds of severe EHI and three-fold when restricting analysis to symptoms before exercise on Day 0. The present findings emphasize the importance of recovery from respiratory infection symptoms before resuming strenuous physical

activity. Participants suffering respiratory infection symptoms three and two days before the loaded march, but who had recovered by Day 0, were no more likely to suffer severe EHI. Respiratory infection symptoms recorded during the monitoring period were not associated with an increased likelihood of mild EHI. Based upon these findings, to minimize the risk of severe EHI, we recommend that individuals suffering respiratory infection symptoms should avoid strenuous physical activity for work or leisure e.g., military personnel and athletes.

Systemic inflammation provides a likely mechanism for the observation that ongoing respiratory infection was associated with severe EHI susceptibility. Infection and associated inflammation, characterized by increases in pyrogenic cytokines (e.g., interleukin (IL)-1ß, IL-6 and Tumor Necrosis Factor-α), may compromise heat tolerance and increase susceptibility to severe EHI (3). The current data demonstrates that participants with respiratory infection symptoms were three times more likely to exhibit systemic inflammation (CRP >3 $mg \cdot L^{-1}$) and had an elevated pre-exercise T_{gi} (Figure 4); albeit, there was no evidence of clinical fever in any participant pre-exercise (≥ 38 °C) (46). The proposed mechanism is consistent with animal studies showing that pre-existing inflammation exacerbates body temperature elevation during heat stress and increases the likelihood and severity of heat stroke (10-12). In humans, inflammation increases body temperature to cause a fever during infection (47) and experimental evidence demonstrates that pre-exercise IL-6 concentration correlates positively with the increase in body temperature during subsequent exercise in the heat (13, 48). Further studies are required to elucidate why respiratory infection was associated with severe but not mild EHI. One possible explanation posited is that mild EHI (often termed exertional heat exhaustion) has a different etiology involving an inability to sustain cardiac output and blood pressure during physical activity (5, 32).

This prospective cohort study has several strengths. First, a comparator control group consisting of all participants who commenced the same exercise bout but did not experience an episode of EHI was included, increasing confidence in the observed association between ongoing respiratory infection symptoms and EHI. Second, to standardize the assessment of CNS disturbance, the key discriminatory feature of severe EHI, we adopted the validated QCS to assess orientation, memory and concentration post-exercise in all conscious participants (19). Third, using the Jackson Common Cold Questionnaire to record daily respiratory infection symptoms is not only practical to implement but also overcomes the limitation that relying on medical records underreports the true incidence of respiratory infection (49). The Jackson Common Cold Questionnaire assesses the clinical features of a common cold and was validated following nasal instillation of common cold secretions in > 1,000 participants (16). Confidence in our respiratory infection assessment is further increased by the findings that respiratory pathogen expression and systemic inflammation were more prevalent in participants with a respiratory infection classification. Fourth, data collection spanned Spring to Fall in the UK ensuring the co-occurrence of EHI and respiratory infection necessary to answer the research question; EHI occurred with similar prevalence across the three seasons and although respiratory infection incidence peaked in the Fall (9%), it also occurred in Spring (5%) and Summer (3%). Fifth, by conducting the study in the temperate UK climate (WBGT range, 4.7–17.4 °C) we were better able to identify the role of respiratory infection and associated inflammation in severe EHI etiology without the independent and overriding influence of extreme environmental heat stress on EHI susceptibility (15). Sixth, fully adjusted logistic regression analyses examining the association between respiratory infection and EHI accounted for other widely considered EHI risk factors e.g., low aerobic fitness (5).

This study is not without limitation. First, the present findings are restricted to the level of association and thus require cautious interpretation. Second, due to the low number of females entering Royal Marine Commando training, the number of females recruited and completing data collection was low (N = 2 of a total sample of N = 807), precluding their inclusion in statistical analyses. Although our sample population was representative of the population of interest, caution is required generalizing these findings drawn from young and otherwise healthy males. As females are considered equally susceptible to respiratory infection and associated inflammation (50, 51) we anticipate that respiratory infection would also be associated with increased severe EHI in females, but this requires confirmation. Third, it was neither practical nor ethical to perform serial blood testing in all participants in the days after the loaded march to assess end-organ damage markers. Notwithstanding, where serial blood samples were available, we found evidence of end-organ damage using clinical thresholds in all cases of severe EHI, increasing confidence in our severe EHI classification. Fourth, as respiratory pathogen detection is variable in clinical common cold presentations (52) we collected respiratory swabs on two separate days before the loaded march (Day -3 and Day -1) but acknowledge we may have missed capturing the causative pathogen in some symptomatic participants, or the causative pathogen might not be included in the Allplex respiratory panel. Fifth, we assessed serum CRP on Day -1 as a measure of systemic inflammation, providing further confidence in our respiratory infection classification; nevertheless, it would have been advantageous to assess circulating pyrogenic cytokines (e.g., IL-6) pre-exercise on Day 0 to capture ongoing inflammation at the time of the loaded march.

The findings of the present study in military recruits performing externally regulated exercise are generalizable to all individuals who undertake strenuous physical activity for work

or leisure (e.g., recreational and elite athletes). Highly motivated recreational and elite athletes performing self-paced exercise are also exposed to the risk of EHI (3, 53) and, like military recruits, against their better judgement frequently engage in strenuous physical activity despite suffering respiratory infection symptoms (54). Choosing to undertake strenuous physical activity when suffering a respiratory infection can impair athletic performance (54), increase the severity and duration of infection (55) and increase the risk of serious medical complications, including myositis, rhabdomyolysis, life-threatening myopericarditis (56, 57) and, as demonstrated herein, severe EHI. We therefore recommend that individuals exposed to an increased risk of EHI (e.g., athletes and military personnel) refrain from strenuous physical activity when suffering a respiratory infection and only resume such activities once symptoms have resolved. Sports federations and authorities responsible for the health and well-being of individuals should consider pre-activity illness symptom screening (e.g., using the Jackson Questionnaire) for activities that present a high risk of EHI. In response to the findings of this study, the UK Ministry of Defence has recently amended its heat illness prevention policy and embedded these recommendations into routine practice (58).

CONCLUSIONS

This prospective cohort study demonstrates that ongoing respiratory infection is associated with an increased likelihood of severe exertional heat illness in military recruits. To minimize the risk of severe exertional heat illness, individuals should avoid strenuous physical activity when suffering respiratory infection symptoms. These findings and practical recommendations are generalizable to all individuals who undertake strenuous physical activity for work or leisure, including recreational and elite athletes.

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FIGURE LEGENDS

Figure 1. Flowchart outlining the number of recruits briefed, assessed for eligibility, consented, completed data collection and included in data analyses.

Figure 2. Study protocol schematic.

Figure 3. Respiratory tract infection (RTI) proximity to the loaded march and association with severe exertional heat illness (EHI). Symptoms of RTI were recorded using the Jackson Common Cold Questionnaire in the three days preceding (Day -3 to Day -1) and before exercise on the day of the 6.4-mile loaded march (Day 0). Presented are fully adjusted odds ratios from logistic regression with 'healthy' as the reference group. Unadjusted odds ratios and 95% confidence intervals from logistic regression analyses are presented in Table 2.

Figure 4. Respiratory tract infection (RTI) symptoms and respiratory pathogen detection (A), systemic inflammation (B) and pre-loaded march gastrointestinal temperature (T_{gi}; C). RTI symptoms were assessed using the Jackson Common Cold Questionnaire. Data are presented in healthy participants and those with RTI symptoms on both Day -1 and Day 0. In panels A and C additional criteria included no evidence of systemic inflammation in 'healthy' (low CRP < 1 $mg \cdot L^{-1}$) and evidence of systemic inflammation in 'RTI' (high CRP > 3 $mg \cdot L^{-1}$), adopting clinically recognized thresholds. T_{gi} data are presented as mean ± SD.

SUPPLEMENTAL DIGITAL CONTENT

SDC1: Supplemental Digital Content.docx

Table 1. Descriptive information by exertional heat illness (EHI) classification. Data are displayed as mean ± SD or N (%).

	Classification		
	Non-EHI N = 632	Mild EHI N = 118	Severe EHI N = 40
Demographic and anthropometry			
Age (years)	22 ± 3	22 ± 3	23 ± 4
Ethnicity, Caucasian	602 (95)	110 (93)	38 (95)
Height (cm)	179.8 ± 6.1	178.7 ± 5.8	179.7 ± 6.1
Body mass (kg)	80.7 ± 7.6	80.6 ± 7.6	81.6 ± 7.9
Factors considered to influence EHI risk			
BMI ($kg \cdot m^{-2}$)	25.0 ± 1.8	25.2 ± 1.9	25.2 ± 2.2
Previous EHI symptoms[1]	67 (11)	27 (23)**	7 (18)
Aerobic fitness (2.5 miles, seconds)	1424 ± 137	1478 ± 147**	1469 ± 127
Non-heat acclimatized	528 (84)	93 (79)	33 (83)
Loaded march WBGT (°C)	10.7 ± 3.5	11.5 ± 3.8	12.5 ± 3.8**
Hydration (Uosm, $mOsmol \cdot kg^{-1}$)	714 ± 233	694 ± 226	695 ± 221
Physician diagnosed illness[2]	30 (5)	6 (5)	1 (3)
Medication[3]	97 (15)	18 (15)	7 (18)
Motivation (score 0–28)	23 ± 3	23 ± 4	23 ± 4

BMI = body mass index; WBGT = wet-bulb globe temperature; Uosm = urine osmolality; [1]Previous EHI symptoms ≤ 2 years; [2]Physician diagnosed respiratory or gastrointestinal illness ≤ 28 days. [3]Medication = prescribed ≤ 28 days or over-the-counter Day 0; ***P* < 0.010 *vs.* non-EHI.

Table 2. Association between respiratory infection and exertional heat illness (EHI).

	Mild EHI	Severe EHI
Day -3 and Day -2		
Unadjusted	1.36 (0.72–2.57), *P* = 0.339	0.97 (0.33–2.84), *P* = 0.958
Fully adjusted[1]	1.47 (0.74–2.93), *P* = 0.275	1.26 (0.39–4.11), *P* = 0.703
Day -1 and Day 0		
Unadjusted	1.17 (0.47–2.89), *P* = 0.739	**2.83 (1.03–7.77), *P* = 0.044**
Fully adjusted	1.23 (0.47–3.22), *P* = 0.673	**4.09 (1.29–12.90), *P* = 0.016**
Day 0		
Unadjusted	1.01 (0.50–2.05), *P* = 0.978	1.98 (0.79–4.94), *P* = 0.143
Fully adjusted	1.04 (0.49–2.20), *P* = 0.893	**2.83 (1.02–7.86), *P* = 0.046**

Presented are odds ratios (95% confidence interval) from logistic regression analyses with 'healthy' as the reference group. [1]Fully adjusted = logistic regression that accounted for: aerobic fitness, duration of the loaded march, WBGT, BMI, hydration status, previous EHI symptoms, heat acclimatization status, motivation, prescribed or over-the-counter medications and hay fever.

Figure 1

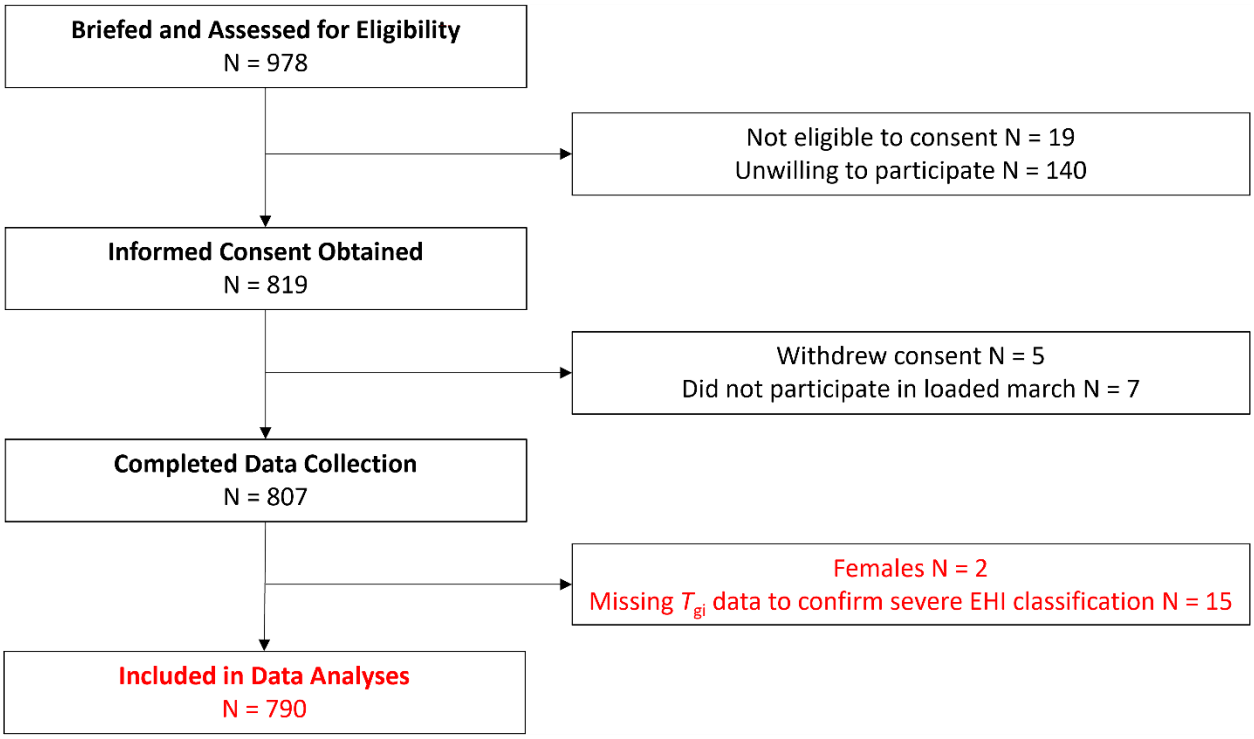

Briefed and Assessed for Eligibility
N = 978
Not eligible to consent N = 19
Unwilling to participate N = 140
Informed Consent Obtained
N = 819
Withdrew consent N = 5
Did not participate in loaded march N = 7
Completed Data Collection
N = 807
Females N = 2
Missing T_{gi} data to confirm severe EHI classification N = 15
Included in Data Analyses
N = 790

Figure 2

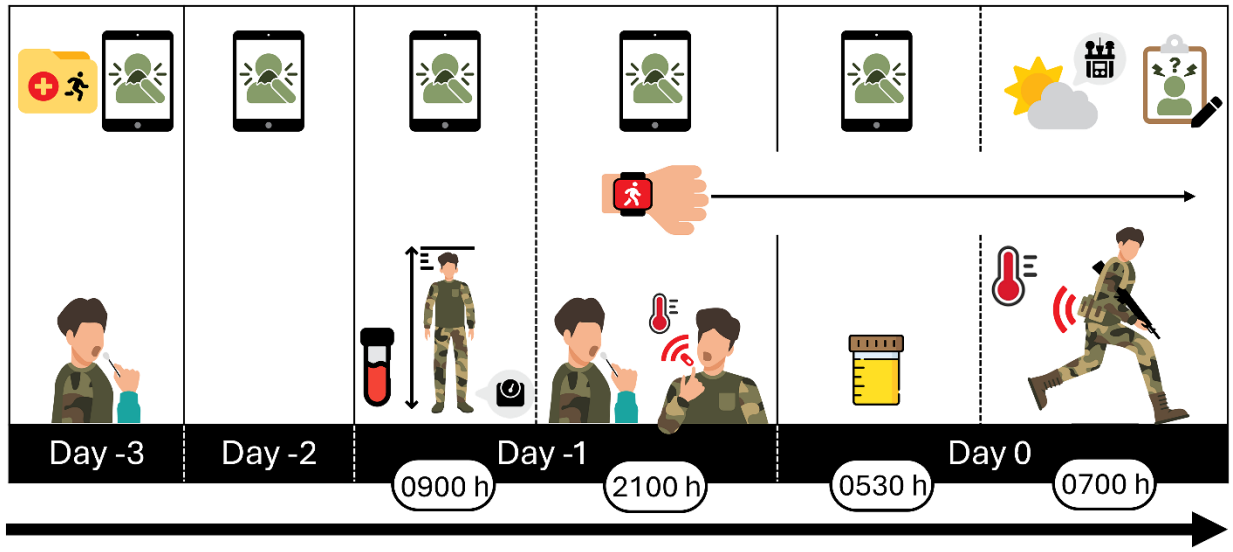


Figure 3

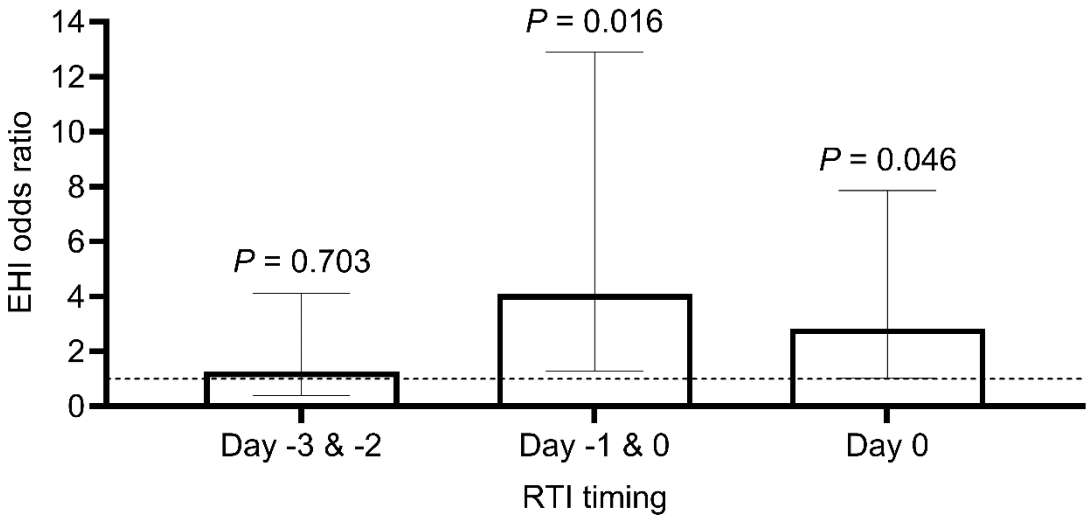
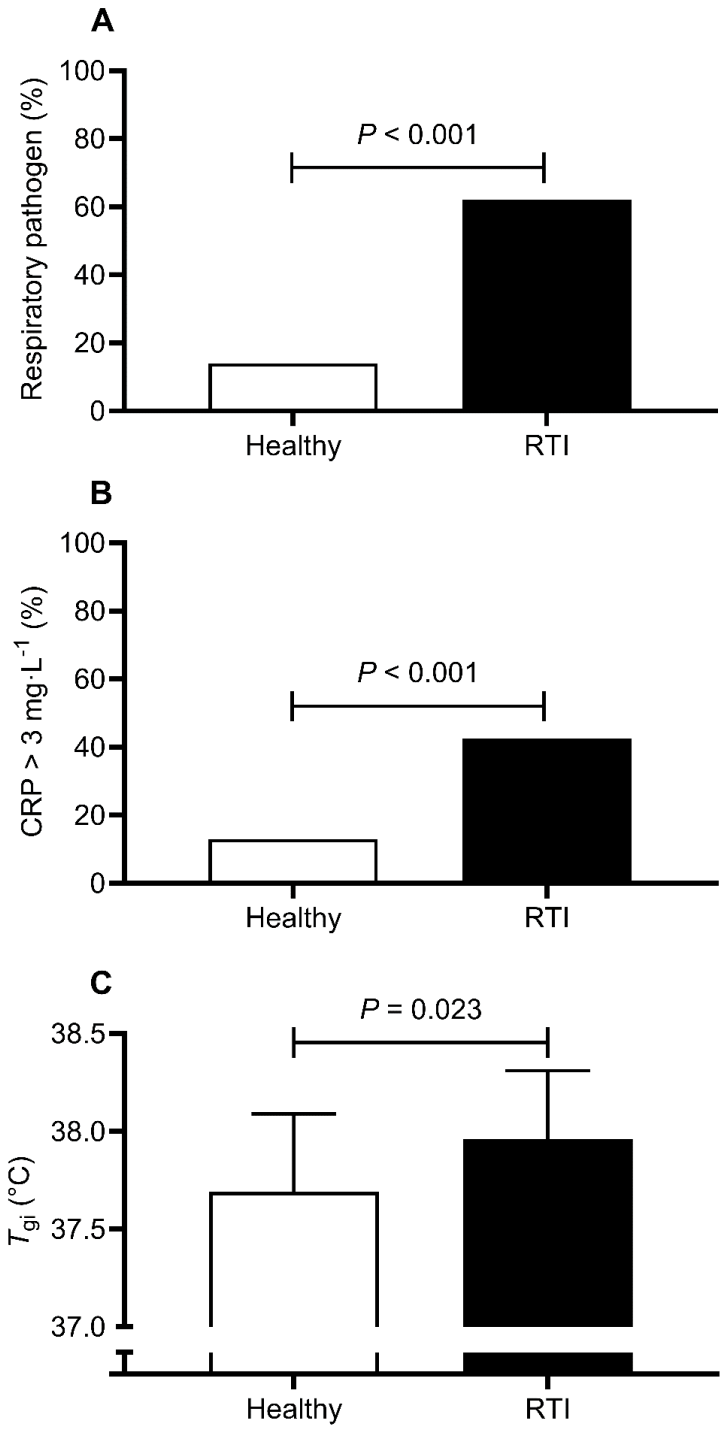

14
12
10
8
6
4
2
0
EHI odds ratio
P = 0.703
P = 0.016
P = 0.046
Day -3 & -2
Day -1 & 0
Day 0
RTI timing

Figure 4


A
Respiratory pathogen (%)
100
80
60
40
20
0
P < 0.001
Healthy
RTI
B
CRP > 3 mg·L-1 (%)
100
80
60
40
20
0
P < 0.001
Healthy
RTI
C
Tgi (°C)
38.5
38.0
37.5
37.0
P = 0.023
Healthy
RTI