PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A Systematic Review of the Gender Differences in the Epidemiology and Risk Factors of Exertional Heat Illness and Heat tolerance in the Armed Forces
AUTHORS	Alele, Faith; Malau-Aduli, Bunmi; Malau-Aduli, Aduli; Crowe, Melissa

VERSION 1 – REVIEW

REVIEWER	William M. Adams, PhD, ATC University of North Carolina at Greensboro, USA
REVIEW RETURNED	28-Jul-2019

GENERAL COMMENTS	The purpose of this systematic review was to describe the epidemiology of heat stroke and other heat-related illnesses between men and women armed forces personnel and to identify predisposing risk factors and gender differences in heat illness and heat tolerance. There are a few concerns that the authors must address within the current manuscript. First, it is not entirely clear why the authors decided to address two specific aims in this review; and while the aims are complimentary, they require a different approach in the procurement of the data as well as the analysis and interpretation. This is evident in the results, particularly when discussing the data on heat intolerance. The authors discuss two studies (Table 3) and in the discussion the authors claim that women are more heat intolerant (and thus more at risk of succumbing to EHI than men). The criteria assessed in the Druyan and Kazman studies were the utilization of the IDF heat tolerance protocol. This test is a Pass/Fail test and the criteria of a rectal temperature >38.5C and HR >155 bpm deem a failure, whereas if an individual did not surpass these thresholds, a passing test. Reporting that women are more heat intolerant than men is incorrect in this instance. While women ended the HTT with a higher HR and rectal temperature, these values still fall below the thresholds needed to deem these individuals as heat intolerant. While there are inherent limitations with this test, it is useful in terms of examining the entire 2 hour exercise bout and determining if there is a plateau of both rectal temperature and HR, which would provide a more accurate depiction of heat intolerance or not. Second, the classification of the data L185-186 inherently increase the variability of the results; data were analyzed/synthesized as either all heat related illness OR heat stroke vs. other heat illnesses. Within the data from the US Armed Forces, the data representing other heat illnesses is vastly different than heat stroke and relies on the coding from ICD-9 or ICD-10. It is

	recommended that the authors further refine their research question to a specific analysis to be able to provide a more thorough presentation and discussion of the data. It is also not clear as to why the Mann-U Whitney test was utilized in this review and the benefit for doing this analysis is versus plotting the data and examining the mean differences and 95% CI. A review of the statistical analysis is warranted.

REVIEWER	Susan Yeargin USA
REVIEW RETURNED	31-Jul-2019

GENERAL COMMENTS	- Title: Armed Forces needs to be included in the title. Please update. - Abstract o Vague criteria and methods- provide some info here from figure 1 o Results- no numbers are provided with the statement in line 55 but this result is a major concluding factor. Please include. o Lines 51-54: this sounds as if it is not a result but methodology. Reword to make it clear that these were significant results from the studies, not just simply factors that the authors looked for while investigating the papers. o Conclusions- please change the wording to better match the conclusion in the manuscript (line 413) to better reflect the results. Current wording seems a bit slanted. - Introduction o Line 81: not all EHI are related to body temperature, update this sentence to be more inclusive. o Line 87: heat cramps are not a commonly used term in the literature anymore, EAMC is. Consider changing terminology. o Lines 81 and 87 make it seems as if EHI are on a continuum which is not accurate, they are all independent injuries/conditions. Please revise wording to make this more clear. o Line 101: how does an elevated temperature lead to heat exhaustion? The definition of heat exhaustion according to ACSM and NATA is “The inability to continue exercise in the heat because of cardiovascular insufficiency” Yes, the person will have an elevated temperature, but that does not cause the heat exhaustion, that is only in the case of heat stroke. If the armed forces definition is different, please reference this. The reference behind the statement does not seem to be a generalized source of EHI definitions. o Line 129: if there is a “dearth” of research on EHI in women in the armed forces, how is this systematic review with 27 studies included possible? It seems that there is plenty of research, they simply haven’t all been systematically reviewed together to provide a conclusive statement. Please reword. - Discussion o Overall the discussion is a little tough to follow. The results are organized by subheadings, why is the discussion not organized by the same headings to help the reader? o Line: 288 and 368-378: Of the two studies included regarding heat tolerance- only one was conducted with a normal population. The other (reference 15) was conducted with heat injury patients. For the latter study, the conclusion is that “women who have sustained a heat injury” had higher heat intolerance rates than men, not just “women”. So, to make the conclusion in the abstract and discussion that “women [in general]” are more heat intolerant is overreaching as only one study found this. Please revise

	statements throughout the paper to be more transparent about the populations of the two studies. o Line 305 (and line 239) heat illness and heat intolerance are clumped together with all the references after the end of the sentence. Please place the correct references behind the appropriate item so its easier for the reader to understand how the authors are reaching this conclusion. o Line 319- what evidence does reference 51 provide to support the statement "decrease heat loss"? Please provide support for that portion of the statement as the reviewer has not seen evidence to indicate that is the reason for increased EHI risk with high BMI individuals. o Line 334- was Australia one of the countries with studies contributing to the findings of this paper? o lines 355-357- did reference 59 indicate that the genetic adaptation was prevalent in a particular ethnic group? Is this truly relevant to the discussion at hand? Please clarify

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Reviewer Name:

William M. Adams, PhD, ATC

Institution and Country:

University of North Carolina at Greensboro, USA

The purpose of this systematic review was to describe the epidemiology of heat stroke and other heat-related illnesses between men and women armed forces personnel and to identify predisposing risk factors and gender differences in heat illness and heat tolerance. There are a few concerns that the authors must address within the current manuscript.

Authors' response: We thank the reviewer for reviewing the manuscript and for the useful feedback. We have revised the manuscript and included the recommended changes.

First, it is not entirely clear why the authors decided to address two specific aims in this review; and while the aims are complimentary, they require a different approach in the procurement of the data as well as the analysis and interpretation. This is evident in the results, particularly when discussing the data on heat intolerance. The authors discuss two studies (Table 3) and in the discussion the authors claim that women are more heat intolerant (and thus more at risk of succumbing to EHI than men). The criteria assessed in the Druyan and Kazman studies were the utilization of the IDF heat tolerance protocol. This test is a Pass/Fail test and the criteria of a rectal temperature >38.5C and HR >155 bpm deem a failure, whereas if an individual did not surpass these thresholds, a passing test. Reporting that women are more heat intolerant than men is incorrect in this instance. While women ended the HTT with a higher HR and rectal temperature, these values still fall below the thresholds needed to deem these individuals as heat intolerant. While there are inherent limitations with this test, it is useful in terms of examining the entire 2 hour exercise bout and determining if there is a plateau of both rectal temperature and HR, which would provide a more accurate depiction of heat intolerance or not.

Authors' response: We have refined our research questions and included more information about heat illness and the role of heat intolerance in the armed forces.

Please see lines 111-114: According to these studies, the heat tolerance test is a useful tool to determine return to duty and to prevent subsequent exertional heat stroke. [8,9] Given that heat stroke may be fatal; it is essential to identify individuals who are at high risk of exertional heat illness. [8]

Lines 131 – 142: However, no systematic review has investigated gender differences among armed forces personnel in relation to heat illness. Given that heat intolerance may predispose to or accompany heat stroke, it is important to understand the role gender plays in heat intolerance.

Therefore, the objective of this systematic review and meta-analysis was to provide a comprehensive summary of the epidemiology of heat illness and heat intolerance in women and men in the armed forces.

Specific aims were

To determine the relative risk of heat illness in women compared to men in the armed forces:

To identify predisposing risk factors associated with heat illness and heat tolerance in the armed forces

We have revised the results and the discussion sections to clarify that both studies reported that more women were classified as heat intolerant compared to men. However, the mean physiological values for all the participants were lower than the test threshold. We acknowledge and have stated that the findings are inconclusive.

Lines 282 – 296:

Two studies compared heat tolerance classification in males and females using the most commonly used test, the HTT developed by the Israeli Defence Force. [13, 49] Druyan et al. investigated gender differences in Israeli Defence Force personnel who had sustained heat injury. The study reported that 67% of the women were found to be heat intolerant compared to 26% of their male counterparts.[13] In the study by Kazman et al. the study population comprised of participants from the university and military communities. The findings of the study reported that a greater proportion of women were classified as heat intolerant compared to men (45% vs 18% respectively). [49] Although the mean physiological parameters for women and men in both studies were below the test threshold (rectal temperature >38.5C and HR >150 bpm); women had higher mean baseline temperature and mean heart rate (Table 3) in both studies [13, 49]. In addition, the mean endpoint heart rates for women were higher compared to their male counterparts.[13, 49] However, the mean end point temperature varied between the two studies; one study reported a higher endpoint temperature for females compared to males [13] and the other study reported similar endpoint temperatures for males and females.[49]

Discussion

Lines 347 -352: Furthermore, despite the higher proportion of heat intolerance reported among women; this finding should be interpreted with caution given the small sample size for females in both studies and the differences in occupations of the women in the two studies. One study included women in the armed forces with a previous history of heat stroke, [13] while the other study recruited women from the general population as well as military members with no previous history of heat stroke [49].

Lines 430 - 437: Although in the two studies, a higher proportion of women were classified as heat intolerant; this evidence should be interpreted with caution given that the female populations included in each study varied with respect to heat illness and occupations. [13, 49] However, both studies acknowledge that gender differences in thermoregulation may account for the higher intolerance rates in women.[13, 49] Furthermore, both studies reported using the Israeli Defence Force heat tolerance test protocol and given that the test protocol was developed using male participants, there may be a need to re-evaluate the criteria for women to reduce false positive results.[13, 49]

Second, the classification of the data L185-186 inherently increase the variability of the results; data were analyzed/synthesized as either all heat related illness OR heat stroke vs. other heat illnesses. Within the data from the US Armed Forces, the data representing other heat illnesses is vastly different than heat stroke and relies on the coding from ICD-9 or ICD-10. It is recommended that the authors further refine their research question to a specific analysis to be able to provide a more thorough presentation and discussion of the data.

Authors' response: We have revised the methods and results sections and reclassified heat illnesses in the review. In addition, we have refined our research questions.

Please see lines 135 -142:

Therefore, the objective of this systematic review and meta-analysis was to provide a comprehensive summary of the epidemiology of heat illness and heat intolerance in women and men in the armed forces.

Specific aims were

To determine the relative risk of heat illness in women compared to men in the armed forces:

To identify predisposing risk factors associated with heat illness and heat intolerance in the armed forces

Methods

Data analysis and synthesis

Please see lines 196 – 222: In this review, the International Classification of Diseases ICD 9 or ICD 10 diagnosis codes [20, 21] for the effects of heat and light were used to classify heat illnesses. All included studies in the review utilized either the ICD 9 or ICD 10 codes to classify heat illnesses depending on the year of publication. Heat illnesses were categorised as all heat illnesses, heat stroke and other heat illnesses (including heat exhaustion and unspecified effects of heat and light). For this analysis, all heat illness was defined as cases where diagnosis of heat stroke (992.0, T67.0), heat exhaustion (992.3–5, T67.3 -5), heat syncope (992.1, T67.1), heat cramps (992.2, T67.2), heat fatigue, transient (992.6, T67.6), heat oedema (992.7, T67.7), other specified heat effects (992.8, T67.8) and unspecified effects of heat and light (992.9, T67.9) were reported. Heat stroke was identified and defined using the ICD diagnosis codes 992.0 (1CD 9) and T67.0 (ICD 10). While other heat illnesses were defined as heat exhaustion (992.3-5, T67 3-5) and unspecified effects of heat and light (992.9 and T67.9). Incidence rates and proportions were extracted from the data reported in each study and used for the analysis in this review. Studies reporting all heat illnesses and the risk factors associated with heat illnesses and heat intolerance were not pooled due to variations in the study designs, populations, and measures reported.

Results

Please see Table 1, supplemental Table 3 and supplemental Table 4

It is also not clear as to why the Mann-U Whitney test was utilized in this review and the benefit for doing this analysis is versus plotting the data and examining the mean differences and 95% CI. A review of the statistical analysis is warranted.

Authors' response: We have revised the statistical analysis and extended the data analysis by conducting a meta-analysis to identify the risk of heat stroke and other heat illness in women compared to men in the armed forces. The title, abstract, methods, results and discussion section have been revised.

Title - Please see lines 1 – 2:

Gender makes the difference in exertional heat illness in the armed forces: A systematic review and meta-analysis.

Lines 41 – 45: Design: Systematic review and meta-analysis.

Data sources and eligibility criteria: A search of multiple databases (MEDLINE, Emcare, CINAHL, PsycINFO, Informit, and Scopus) was conducted from inception of the databases to 1st April 2019 for studies investigating and comparing heat illness and heat tolerance in women and men in the armed forces.

Lines 46– 50: Twenty-seven (27) studies were included in the systematic review and 13 of these studies were included in the meta-analysis. Meta-analysis of the 13 studies identified a 43% decreased risk of heat stroke in women compared to men (risk ratio = 0.56, 95% CI 0.47 to 0.66). The overall risk of other heat illnesses (heat exhaustion and unspecified effects of heat and light) was 26% higher in women compared to men (risk ratio = 1.26, 95% CI 1.15 to 1.38).

Please see lines 211 – 222:

A meta-analysis was conducted to provide an overview of the risk of heat stroke and other heat illnesses (heat exhaustion and unspecified effects of heat) in women compared to men in the armed forces. A pooled analysis of the risk of heat stroke was conducted separately from other heat illnesses. For other heat illnesses, a subgroup analysis was performed according to classifications used in the included studies (1 – heat exhaustion and unspecified effects of heat and light and 2 – heat exhaustion). The risk ratio for each study and the pooled risk ratios (RR) with 95% CI were calculated using Review Manager 5.3. [22[The risk ratios were presented as the ratio of the incidence rates of heat illness in women to men. A random effects model was used, taking into account the heterogeneity of the included studies. I2 was used to measure the heterogeneity (between study variations) of the included studies. Where the percentage of variation between the included studies was greater than 50%, a sensitivity analysis was performed.

Results

Please see lines 301 – 318:

Meta-analysis findings

Of the 27 studies, 13 were included in the meta-analysis. The incidence rate data were extracted from the included studies and pooled together to perform the meta-analysis (Supplemental Table 3 and Supplemental Table 4).

Risk of heat stroke in women and men in the armed forces

In the pooled analysis, the risk ratio of heat stroke in women compared to men in the armed forces was 0.56 (95% CI 0.47 to 0.66). There was no heterogeneity (I2 = 0%) in the studies reporting heat stroke (Figure 2).

Risk of other heat illnesses in women and men in the armed forces

The overall pooled risk ratio of other heat illness was 1.26 (95% CI 1.15 to 1.38) in women compared to men in the armed forces (Figure 3). The women to men risk ratio of studies reporting heat exhaustion and unspecified effects of heat and light was 1.28 (95% CI 1.14, to 1.45). In studies reporting only heat exhaustion, the risk of heat exhaustion in women compared to men was 1.22 (95% CI 1.06 to1.42). The percentage of variance between the included studies due to heterogeneity (I2) was 53%; a sensitivity analysis was conducted where three of the included studies with the largest rates: AMSA 2006, AMSA 2012, and AMSA 2013 [36, 42, 43] were excluded. The heterogeneity test was lower (I2 = 7%) after excluding the studies from the pooled analysis (Supplemental Figure 1), however the effect did not change (pooled RR = 1.18, 95% CI 1.09 to 1.27).

Discussion

Lines 333 – 342: This systematic review and meta-analysis provide an overview on the available evidence on epidemiology of heat illnesses and heat tolerance in women compared to men in the armed forces.

Summary of findings

The findings of this systematic review suggest a higher rate of all heat illnesses (defined as cases where a combined diagnosis of all heat illnesses was reported) in men compared to women as evidenced by the outcomes reported in six (6) of eight (8) studies. The meta-analysis of 13 studies demonstrated that women had 44% less risk of heat stroke compared men in the armed forces. On the other hand, the overall pooled analysis revealed that women had 26% increase in risk of other heat illnesses (heat exhaustion and unspecified heat illnesses).

Figure 2 and Figure 3.

Reviewer: 2

Reviewer Name: Susan Yeargin

Institution and Country: University of South Carolina

- Title: Armed Forces needs to be included in the title. Please update

Authors' response: We thank the reviewer for her kind comment. We have updated the title.

Please see lines 1 – 2: Gender makes the difference in exertional heat illness in the armed forces: A systematic review and meta-analysis.

- Abstract

o Vague criteria and methods- provide some info here from figure 1

Authors' response: We have revised the abstract to include more information about the criteria and method used. We have now included a meta-analysis in the review in response to comments from reviewer 1 and included these details in the methods section of the abstract.

Please see lines 41 – 45:

Design: Systematic review and meta-analysis.

Data sources and eligibility criteria: A search of multiple databases (MEDLINE, Emcare, CINAHL, PsycINFO, Informit, and Scopus) was conducted from inception of the databases to 1st April 2019 for studies investigating and comparing heat illness and heat tolerance in women and men in the armed forces.

o Results- no numbers are provided with the statement in line 55 but this result is a major concluding factor. Please include.

Authors' response: We have revised the abstract and rewritten the statement to align with the current results.

Please see lines 53 – 54: Although there was a higher proportion of women who were heat intolerant compared to men; this finding needs to be interpreted with caution due to the limited evidence.

o Lines 51-54: this sounds as if it is not a result but methodology. Reword to make it clear that these were significant results from the studies, not just simply factors that the authors looked for while investigating the papers.

Authors' response: We have revised the statement.

Please see lines 51- 53: The factors significantly associated with heat illness were gender, age, level of education, ethnicity, body mass index (BMI), positive sickle cell trait, being in service for less than 1 year, and unit of service.

o Conclusions- please change the wording to better match the conclusion in the manuscript (line 413) to better reflect the results. Current wording seems a bit slanted.

Authors' response: We have rewritten the conclusion.

Please see lines 55 – 58: In relation to armed forces personnel, the findings of this review suggest that men experienced a higher risk of heat stroke than women. However, women have a greater risk of other heat illnesses. Despite the limited evidence, further research is required to investigate the influence of gender differences on heat intolerance and heat illness.

- Introduction

o Line 81: not all EHI are related to body temperature, update this sentence to be more inclusive.

Authors' response: We have updated the sentence. Please see lines 81 – 82:

Heat illnesses are disorders that arise after prolonged exposure to heat/humidity and/or increased physical activity.[1]

o Line 87: heat cramps are not a commonly used term in the literature anymore, EAMC is. Consider changing terminology.

Authors' response: We have changed the terminology to exercise-associated muscle cramps (EAMC).

Please see lines 85 – 87: Without adequate cooling, heat illnesses may occur including exercise-associated muscle cramps (EAMC), heat syncope, heat exhaustion and heat stroke, a potentially life-threatening disorder.[1]

o Lines 81 and 87 make it seems as if EHI are on a continuum which is not accurate, they are all independent injuries/conditions. Please revise wording to make this more clear.

Authors' response: We have revised the statement.

Please see lines 85 – 87: Without adequate cooling, heat illnesses may occur including exercise-associated muscle cramps (EAMC), heat syncope, heat exhaustion and heat stroke, a potentially life-threatening disorder.[1]

o Line 101: how does an elevated temperature lead to heat exhaustion? The definition of heat exhaustion according to ACSM and NATA is "The inability to continue exercise in the heat because of cardiovascular insufficiency" Yes, the person will have an elevated temperature, but that does not cause the heat exhaustion, that is only in the case of heat stroke. If the armed forces definition is different, please reference this. The reference behind the statement does not seem to be a generalized source of EHI definitions.

Authors' response: We have revised the statement and included an appropriate reference.

Please see lines 98 – 101: Individuals who are unable to cope with heat stress may be affected by heat exhaustion or heat stroke as a result of a combination of factors including an elevation in body temperature, cardiovascular insufficiency, hypotension and fatigue [7].

o Line 129: if there is a "dearth" of research on EHI in women in the armed forces, how is this systematic review with 27 studies included possible? It seems that there is plenty of research, they simply haven't all been systematically reviewed together to provide a conclusive statement. Please reword.

Authors' response: We have reworded the statement.

Please see lines 131 – 133: However, no systematic review has investigated gender differences among armed forces personnel in relation to heat illness and heat intolerance.

- Discussion

o Overall the discussion is a little tough to follow. The results are organized by subheadings, why is the discussion not organized by the same headings to help the reader?

Authors' response: We have included sub-headings in the discussion.

Please see lines 336, 353, 375 and 426.

o Line: 288 and 368-378: Of the two studies included regarding heat tolerance- only one was conducted with a normal population. The other (reference 15) was conducted with heat injury patients. For the latter study, the conclusion is that "women who have sustained a heat injury" had higher heat intolerance rates than men, not just "women". So, to make the conclusion in the abstract and discussion that "women [in general]" are more heat intolerant is overreaching as only one study found this. Please revise statements throughout the paper to be more transparent about the populations of the two studies.

Authors' response: We have revised this finding and included the changes in the abstract, results and discussion sections.

Please see Abstract lines 53 – 54:

Although there was a higher proportion of women who were heat intolerant compared to men; this finding needs to be interpreted with caution due to the limited evidence.

Lines 55 – 58:

Abstract Conclusion:

In relation to armed forces personnel, the findings of this review suggest that men experienced a higher risk of heat stroke than women; however, women may have a greater risk of other heat illnesses. Despite the limited evidence, further research is required to investigate the influence of gender differences on heat intolerance and heat illness.

Results

Lines 282 – 299:

Two studies compared heat tolerance classification in males and females using the most commonly used test, the HTT developed by the Israeli Defence Force. [13, 49] Druyan et al. investigated gender differences in Israeli Defence Force personnel who had sustained heat injury. The study reported that 67% of the women were found to be heat intolerant compared to 26% of their male counterparts.[13] In the study by Kazman et al. the study population comprised of participants from the university and military communities. The findings of the study reported that a greater proportion of women were classified as heat intolerant compared to men (45% vs 18% respectively). [49] Although the mean physiological parameters for women and men in both studies were below the test threshold (rectal temperature >38.5C and HR >150 bpm); women had higher mean baseline temperature and mean heart rate (Table 3) in both studies [13, 49]. In addition, the mean endpoint heart rates for women were higher compared to their male counterparts.[13, 49] However, the mean end point temperature varied between the two studies; one study reported a higher endpoint temperature for females compared to males [13] and the other study reported similar endpoint temperatures for males and females.[49]

Discussion

Lines 347 -352: Furthermore, despite the higher proportion of heat intolerance reported among women; this finding should be interpreted with caution given the small sample size for females in both studies and the differences in occupations of the women in the two studies. One study included women in the armed forces with a previous history of heat stroke, [13] while the other study recruited women from the general population as well as military members with no previous history of heat stroke.[49]

Lines 430 - 437: Although in the two studies, a higher proportion of women were classified as heat intolerant; this evidence is should be interpreted with caution given that the female population included in each study varied from the other due to differences in exposure to heat and occupations.[13, 49] However, both studies acknowledge that gender differences in thermoregulation may account for the higher intolerance rates in women.[13, 49] Furthermore, both studies reported using the Israeli Defence Force heat tolerance test protocol and given that the test protocol was developed using male subjects, there may be a need to re-evaluate the criteria for women to reduce false positive results.[13, 49]

o Line 305 (and line 239) heat illness and heat intolerance are clumped together with all the references after the end of the sentence. Please place the correct references behind the appropriate item so its easier for the reader to understand how the authors are reaching this conclusion.

Authors' response: We have revised the manuscript to clearly link the relevant references to each topic and the risk factors associated with heat illness and heat tolerance.

Please see lines 257 – 265:

As shown in Table 2, five (5) studies identified the risk factors associated with heat illness,[23, 27, 30, 31, 48] while one (1) study identified the predictors of heat tolerance.[49] Of the five (5) studies reporting the risk factors associated with heat illness, one study identified the risk for heat illness in association with SCT status.[23] The odds of females experiencing heat illness ranged from 1.04 to 1.5 compared to males.[23, 27, 30, 31] Other identified risk factors for heat illness (Table 2) included younger and older age,[23, 27] lower level of education,[27] ethnicity,[27, 30] higher body mass index (BMI),[48] being SCT positive,[23] being in service for less than 1 year,[27] and serving in combat units as an infantry or gun crew soldier.[27, 30] The factor that predicted heat intolerance was lower VO2max.[49]

Please see lines 365 – 366: However, despite the lower risk of heat stroke, women had a greater risk of other heat illnesses (heat exhaustion and unspecified effects of heat and light) than men. [32, 36 – 47]

o Line 319- what evidence does reference 51 provide to support the statement "decrease heat loss"? Please provide support for that portion of the statement as the reviewer has not seen evidence to indicate that is the reason for increased EHI risk with high BMI individuals.

Authors' response: We have revised the statement.

Please see lines 379 - 381: Evidence suggests that individuals with higher BMI (indicating higher body fat) have been reported to be at increased risk of exertional heat illness and are less heat tolerant.[52]

o Line 334- was Australia one of the countries with studies contributing to the findings of this paper?

Authors' response: Australia was not one of the countries contributing to the review. We discussed the findings in relation to previous studies.

Please see lines 392 – 397: The association between shorter duration in service and the increased risk of heat illness was inconclusive given that only one study investigated and reported its findings. However, the findings are in contrast to a previous study that reported that individuals with more years of service in the army had poorer physiological characteristics (lower aerobic capacity, lower maximum heart rate and higher percentage body fat).[56] These poorer physiological characteristics may place armed forces personnel at risk of heat illness.[52, 53]

o lines 355-357- did reference 59 indicate that the genetic adaptation was prevalent in a particular ethnic group? Is this truly relevant to the discussion at hand? Please clarify

Authors' response: We have included the appropriate reference and reworded the statement to explain the potential reasons for ethnic differences.

Please see lines 412 – 415: The association between ethnicity and heat illness is not fully understood and other factors like acclimatisation and genetic adaptation may play a role in the differences between ethnic groups.[59]

VERSION 2 – REVIEW

REVIEWER	William M. Adams, PhD, ATC University of North Carolina Greensboro, USA
REVIEW RETURNED	06-Oct-2019

GENERAL COMMENTS	The reviewer appreciates the author's revision and accompanying response to the reviewer. While the authors have responded to the reviewer's concerns, there are still some concerns that were not addressed in the revision. 1) It is still not clear as to why the author's are deciding to approach two separate aims within this review. The authors are looking to answer two, although related in topic, separate in scope. This prevents the authors from making a more rigorous approach in their study selection and inclusion. On Lines 226-239, the authors outline their systematic process in selecting the articles, and from the 27 that were included, there were inconsistencies in types of articles selected. For example, the authors included a study examining heat illness in a population that had SCT. It has been known since the 1980's that those that are SCT positive (a small proportion of the Armed Forces Population), have a 35 times greater risk of death (including being caused by EHS), than the rest of the population. It is not clear how this study is representative of the purpose of this paper. Further, since the included studies cover a number of specific topics (L234-239), it is unclear as to the justification of performing a meta-analysis,

	particularly given the large heterogeneity values calculated from some of the analyses. 2) Within the Data Analysis and Synthesis section, the authors classification of heat illnesses present an issue. The categorization was heat illness, heat stroke, and other heat illnesses. The categorization of the conditions representative of the heat stroke and other heat illness categories are also embedded within the heat illness category, thus this data is counted twice. It is strongly suggested that categorizing as either heat stroke or other heat illnesses is the most appropriate, particularly how "other heat illnesses" are assessed within the Armed Forces, and the changes in classification that have occurred in the Armed Forces in the "other" category in the last 5 reporting years (US Armed Forces data, which is included in this study). Furthermore, on Line 209, the authors state that risk factors related to heat illnesses were not pooled, however, on Line 212, the authors state that this data was pooled, and the data presented in the results shows pooled data. 3) The authors have decided to leave the discussion related to heat intolerance between men and women in the study. Although the authors have described the failure rate of the IDF HTT in men vs. women, the further discussion of the physiological response does not present a clinically meaningful discussion. For example, baseline Trec was higher in women and men, however, this was by less than 0.2C and could be explained by intraindividual variability. Furthermore, claiming that women had a higher ending Trec and HR (using this to support heat intolerance), does not fully contextualize the use of the IDF HTT, which these two studies used. the IDF HTT uses a fixed intensity as its protocol, meaning that the overall relative intensity (the primary driver for metabolic heat production) is greater in women than men. This is most likely the reason why the differences in failure rates exist....women are required to perform exercise at a greater relative intensity then men, thus producing more body heat. 4) Within the discussion, the authors aim to discuss the differences in heat illnesses in women compared to men. The discussion on lines 354-355 as well as the supporting discussion below (L356-364) is inherently flawed. The specific occupations within the Armed forces in which women and men have are different. Until recently (within the last 1-2 years), women have been prevented from serving in certain roles (infantry, special operations, etc.), and given the demands of these specific job roles, men would have a higher EHS rate. Furthermore, the discussion on Lines 365-370 is not fully representative of the published literature on this topic. Early literature examining thermoregulatory differences between men and women have shown that the sweating responses and cutaneous vasodilation responses were primarily responsible for differences in thermoregulation. Contemporary literature has shown that differences in thermoregulation across the menstrual cycle are subtle and are nullified when factoring in the extent of environmental stress and/or behavioral responses. It must be further noted, that there are limitations in interpreting some of this literature (controlled laboratory studies) into field-based settings as the results between these two studies are conflicting. 5) L376-425 discuss risk factors regarding heat illness, however, these are not specific to gender, the purpose of this study.

REVIEWER	Susan Yeargin University of South Carolina
REVIEW RETURNED	10-Sep-2019

GENERAL COMMENTS	The authors did a very good job addressing all of my initial concerns as well as addressing the concerns of the author reviewer. I have no further suggestions or revisions.

REVIEWER	Dr. Sharoon Hanook Forman Christian College (A Chartered University) Lahore Pakistan
REVIEW RETURNED	30-Nov-2019

GENERAL COMMENTS	1. I wonder if the researcher has studied the agreement among the various reported studies. 2. I am unable to understand the point of having table 2 and table 3, this does not answer the research question. A lot of tables should be either omitted or reorganized to bring more consistency and clarity in reporting arguments. 3. In the PRISMA Checklist authors says Subgroup analysis to be “NA” but in line 213 it is discussed and reported in supplementary figure 1. Moreover, in the subgroup analysis both the categories are not mutually exclusive, as Heat exhaustion is considered in both the factors used to carry out subgroup analysis, wondering if there was any duplication of the data? Please clarify? 4. Subgroup analysis in Figure 3 shows moderate to high heterogeneity among the studies. Researchers need to consider this while concluding the research. 5. Supplementary Table 3 shows zero QATSDD scores for three studies and very low score for many for the many studies, if there was no relevance of these studies with the objectives and other aspects of the study then shouldn’t these studies be excluded from the Meta-Analysis. 6. Please check why in the overall analysis the Risk Ratios (figure 2) favors women but in the subgroup analysis (figure 3) risk ratios favor men? 7. There should be more clarity that how the data were categorized into various categorize described in lines 195 – 206. 8. The figure at Page 49, has no information that why it has been reported, I also present subgroup analysis that is reported in Figure 3 8. I agree with the comments of the other reviewer that states. "Within the Data Analysis and Synthesis section, the authors classification of heat illnesses present an issue. The categorization was heat illness, heat stroke, and other heat illnesses. The categorization of the conditions representative of the heat stroke and other heat illness categories are also embedded within the heat illness category, thus this data is counted twice. It is strongly suggested that categorizing as either heat stroke or other heat illnesses is the most appropriate, particularly how "other heat illnesses" are assessed within the Armed Forces, and the changes in classification that have occurred in the Armed Forces in the "other" category in the last 5 reporting years (US Armed Forces data, which is included in this study). Furthermore, on Line 209, the authors state that risk factors related to heat illnesses were not pooled, however, on Line 212, the authors state that this data was pooled, and the data presented in the results shows pooled data."

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name

Susan Yeargin

Institution and Country

University of South Carolina

Please state any competing interests or state 'None declared':

None declared

Please leave your comments for the authors below The authors did a very good job addressing all of my initial concerns as well as addressing the concerns of the author reviewer. I have no further suggestions or revisions.

We thank the reviewer for her kind comment.

Reviewer: 1

Reviewer Name

William M. Adams, PhD, ATC

Institution and Country

University of North Carolina Greensboro, USA

Please state any competing interests or state 'None declared':

None declared

Please leave your comments for the authors below

The reviewer appreciates the author's revision and accompanying response to the reviewer. While the authors have responded to the reviewer's concerns, there are still some concerns that were not addressed in the revision.

We thank the reviewer for his comments.

1) It is still not clear as to why the author's are deciding to approach two separate aims within this review. The authors are looking to answer two, although related in topic, separate in scope. This prevents the authors from making a more rigorous approach in their study selection and inclusion.

We chose to conduct a systematic review with both aims because they are complimentary as noted by the reviewer. Exertional heat illness is a global topical issue particularly from the military perspective. When an individual experiences heat illness, it doesn't stop there. Return to duty has to be determined and according to O'Connor et al. (2018) determining return to play (for athletes) or return to duty can be challenging for clinicians. While there are no evidence-based recommendations, the American College of Sports Medicine has published recommendations that include the use of a laboratory exercise heat tolerance test if return to vigorous activity has not commenced within 4 weeks. While we acknowledge that the Israeli Defence Force heat tolerance test is not used by the United States military as part of the return to duty process, it does not negate the fact that it is being used by other Defence Forces in other parts of the world. Our systematic review was conducted to obtain a global perspective of exertional heat illnesses, risk factors and heat tolerance in females compared to males in the armed forces. Women in the armed forces are at an increased risk of experiencing heat illness in comparison to their male counterparts. Furthermore, if they are subjected to the heat tolerance test as part of the return to duty process, they may be at a disadvantage given that the protocol was developed among male participants. We understand that the economic burden as well as the defence operational implications of heat illness is significant. If a female participant is considered heat intolerant, the operational implications as well as career implications for the participant may be negative. Therefore, we decided to conduct a systematic review to identify what has been published about gender differences in relation to heat illness and heat tolerance. We only included articles that investigated heat illness, as well as gender specific risk factors and heat tolerance in the armed forces. We acknowledge the reviewer's concern and to ensure that we did not miss potental articles, we used a broad search strategy that encompassed heat illness and heat tolerance. We have reviewed our search to ensure all articles that were previously omitted are now included in the review.

To explain the relationship between both aims, we have revised the introduction to reflect the relationship and the underlying importance of the study.

Introduction

Please see lines 110 - 151

When exertional heat illness occurs, it may be challenging to determine if an individual may return to duty. An inaccurate determination of complete recovery among armed forces personnel may negatively impact military readiness.[14] While, there are no evidence-based recommendations for return to duty, the American College of Sports Medicine (ACSM) guidelines states that exertional heat stroke patients may return to duty after re-establishing heat tolerance.[15] However, individuals vary in their ability to cope with heat stress and the inability to withstand heat stress during exertion in hot environments is defined as heat intolerance.[2] Evidence suggests that heat intolerance may be a direct result of heat stroke or due to predisposing inherent factors (genetics).[2] However, the objective criteria or measure for defining heat tolerance or intolerance remains a subject of controversy.[14] The current return to duty guidelines for military personnel varies across countries.[16] For example, in the United States, military return to duty process is based on clinical assessments with gradual acclimatization and re-introduction of duties.[17] By contrast, return to duty in the Israeli Defence Force requires a heat tolerance test to determine if an individual is heat tolerant.[18] Therefore, it is important to develop evidence based return to duty protocols across the globe.

The Israeli Defence Force originally developed the heat tolerance test in 1979 as an index of the ability of soldiers to cope with exertional heat.[18] Individuals who have suffered heat stroke are sent for a heat tolerance test after a minimum recovery period of 6 to 8 weeks as part of the return to duty process.[18] Criteria used to define heat intolerance include an elevation in rectal temperature above 38.5°C and heart rate above 150 bpm or when rectal temperature or heart rate fail to stabilize during the test. The heat tolerance test criteria are based on previous studies by Shapiro et al.[19] which utilised only male military participants.[18, 19] While the test may be considered as a useful tool to determine return to duty and to prevent subsequent exertional heat stroke, [18,19] there is no consensus on the validity of the tool as a diagnostic test for heat tolerance.[14] Furthermore, the heat tolerance test does not account for predicting factors such as gender.[14] Given the limitation, there have been questions raised about the validity of the protocol in determining return to duty for females in the armed forces. It has been suggested that more research is required to determine whether or not a new protocol should be developed for women.[12]

As restrictions on gender based exclusions from military specializations are lifted,[20], it is imperative to understand and evaluate exertional heat illness in women compared to men and identify the gender specific risk factors. Furthermore, it is important to understand how women respond to the heat tolerance test compared to men. According to a recent review on the risk of heat illness in women compared with men in the general population, men are at increased risk of heat illness compared to women.[21] However, no previous review has investigated the epidemiology and risk factors of heat illness as well as gender responses to the heat tolerance test in men and women in the armed forces. Given that, heat illness can impact defence operational effectiveness and may result in acute loss of manpower and possible medical discharge from service,[22] it is essential that the review should be conducted to inform policies.

Therefore, the objective of this systematic review was to provide a comprehensive summary of the epidemiology of heat illness and heat intolerance in women and men in the armed forces.

On Lines 226-239, the authors outline their systematic process in selecting the articles, and from the 27 that were included, there were inconsistencies in types of articles selected. For example, the authors included a study examining heat illness in a population that had SCT. It has been known since the 1980's that those that are SCT positive (a small proportion of the Armed Forces Population), have a 35 times greater risk of death (including being caused by EHS), than the rest of the population. It is not clear how this study is representative of the purpose of this paper.

We have excluded the paper describing heat illness among Armed Forces personnel with SCT to ensure consistency and applicability.

Further, since the included studies cover a number of specific topics (L234-239), it is unclear as to the justification of performing a meta-analysis, particularly given the large heterogeneity values calculated from some of the analyses.

Initially, we did not perform a meta-analysis because we considered the included studies to be heterogeneous. However, when the reviewer in his first review made a comment about plotting means rather than conducting a Man-Whitney U test, we sought statistical advice and we interpreted the reviewer’s request as conducting a meta-analysis. Now that we understand this was not the recommendation, we have returned to the original format and excluded the meta-analysis and only reported the findings of the systematic review. Furthermore, we have presented the incidenceates of heat stroke and other heat illnesses using bar charts.

Please see the sections listed below

Methods

Lines 208 - 219

Data analysis and synthesis

In this review, the International Classification of Diseases ICD 9 or ICD 10 diagnosis codes [25, 26] for the effects of heat and light were used to classify heat illnesses. All included studies utilized either the ICD 9 or ICD 10 codes to classify heat illnesses depending on the year of publication. Heat illnesses were categorised as heat stroke and other heat illnesses (including heat exhaustion and unspecified effects of heat and light). Heat stroke was identified and defined using the ICD diagnosis codes 992.0 (1CD 9) and T67.0 (ICD 10). While other heat illnesses were defined as heat exhaustion (992.3-5, T67 3-5) and unspecified effects of heat and light (992.9 and T67.9). In addition, some studies presented findings for all heat illness without categorizing them into heat stroke and other heat illnesses. These findings were presented separately. Incidence rates and proportions were extracted from the data reported in each study and used for the analysis in this review.

Results

Lines 223 – 250

An initial search identified 3801 papers. After removing duplicates, screening titles and abstracts, 47 papers remained for full text review with twenty-four (24) included in the systematic review (Figure 1). Twenty-two (22) of the reviewed articles originated from the United States of America (USA), while the other two studies were conducted in the United Kingdom (UK) and Israel respectively (Supplemental Table 2). All included studies were conducted among armed forces personnel, however, two studies included university staff and armed forces personnel in the studies.[27, 28] Twenty- one (21) articles examined heat illnesses and injuries in women and men. Seven (7) of these studies described all heat related illnesses in men and women,[29-35] while 13 studies included information on heat stroke and other heat injuries in relation to both genders.[36-48] Four (4) studies identified gender specific risk factors associated with heat stroke,[31, 34, 35, 49] and three (3) studies compared heat tolerance in men and women.[12, 27, 28]

Incidence of heat stroke in women compared to men in the armed forces

Thirteen studies conducted among US army personnel compared the incidence of heat stroke between men and women.[36 – 48] The incidence of heat stroke among females ranged from 0.10 to 0.26 per 1000 person years. Among males, the incidence of heat stroke ranged from 0.22 to 0.48 per 1000 person years (Figure 2). Between 2015 and 2018, the incidence of heat stroke increased steadily for both men and women.

Incidence of other heat illnesses in women compared to men in the armed forces

The incidence of other heat illnesses was reported by 13 studies conducted by the US Army. The incidence of other heat illnesses in women ranged from 1.30 to 2.89 per 1000 person years. In men, the incidence rate of other heat illness ranged from 0.98 to 1.98 per 1000 person years (Figure 3).

Incidence and prevalence of all heat illnesses in women compared to men

Table 1 shows the proportions and incidences of all heat-related illness in men and women in the armed forces. Five (5) studies reported higher incidences and proportions of all heat illness in men compared to women[29, 31, 32, 34, 35] while two studies reported higher incidences of all heat illness in women.[30, 33]

Please see Figure 2 and Figure 3

2) Within the Data Analysis and Synthesis section, the authors classification of heat illnesses present an issue. The categorization was heat illness, heat stroke, and other heat illnesses. The categorization of the conditions representative of the heat stroke and other heat illness categories are also embedded within the heat illness category, thus this data is counted twice.

It is strongly suggested that categorizing as either heat stroke or other heat illnesses is the most appropriate, particularly how "other heat illnesses" are assessed within the Armed Forces, and the changes in classification that have occurred in the Armed Forces in the "other" category in the last 5 reporting years (US Armed Forces data, which is included in this study).

We have revised the methods and categorized heat illness as heat stroke or other heat illness. However, there were seven articles that described all heat related illness wherein heat stroke and

other categories were included and not differentiated. We presented
and discussed these findings separately. For clarity, we presented the incidence of heat stroke, incidence of other heat illnesses and the incidence and proportion of all heat illnesses separately. Papers that discussed all heat illnesses were not included in the narrative synthesis of heat stroke or other heat illnesses.

Please see lines 208 - 219

Data analysis and synthesis

In this review, the International Classification of Diseases ICD 9 or ICD 10 diagnosis codes [25, 26] for the effects of heat and light were used to classify heat illnesses. All included studies utilized either the ICD 9 or ICD 10 codes to classify heat illnesses depending on the year of publication. Heat illnesses were categorised as heat stroke and other heat illnesses (including heat exhaustion and unspecified effects of heat and light). Heat stroke was identified and defined using the ICD diagnosis codes 992.0 (1CD 9) and T67.0 (ICD 10). While other heat illnesses were defined as heat exhaustion (992.3-5, T67 3-5) and unspecified effects of heat and light (992.9 and T67.9). In addition, some studies presented findings for all heat illness without categorizing them into heat stroke and other heat illnesses. These findings were presented separately. Incidence rates and proportions were extracted from the data reported in each study and used for the analysis in this review.

Furthermore, on Line 209, the authors state that risk factors related to heat illnesses were not pooled, however, on Line 212, the authors state that this data was pooled, and the data presented in the results shows pooled data.

We have excluded the meta-analysis from the manuscript. This statement has therefore been deleted from the manuscript. We have presented a narrative synthesis of the findings in the result section.

Please see lines 256 – 267

Gender specific risk factors for heat illness

Three (3) studies identified the gender specific risk factors that were associated with heat illness (Table 2). [31, 34, 49] Two of the studies compared the risk of heat illness between males and females while one study identified risk factors within each gender. In the two studies that compared the risk of heat illness by gender, females had a greater risk of experiencing heat illness (OR 1.5 95% CI 1.4 – 1.7 and IDR 1.21 95% CI 1.09 – 1.40) compared to males.[31, 34] Within gender, males with body mass index (BMI) of ≥ 26 kgm^{-2} had a greater risk of experiencing heat illness compared to males with BMI < 22 kgm^{-2} (OR 2.10 95% CI 1.59 – 2.78).[49] In addition, males with run times of ≥ 12.9 minutes had almost six times greater risk of exertional heat illness compared to run times of < 10.3 minutes (OR 5.61 95% CI 1.92 – 6.85). While females with run times of ≥ 6.9 minutes had five times greater risk of exertional heat illness compared to females with run times of < 5.8 minutes (OR 5.30 95% CI 1.59 -17.64).[49]

3) The authors have decided to leave the discussion related to heat intolerance between men and women in the study. Although the authors have described the failure rate of the IDF HTT in men vs. women, the further discussion of the physiological response does not present a clinically meaningful discussion. For example, baseline Trec was higher in women and men, however, this was by less than 0.2C and could be explained by intraindividual variability. Furthermore, claiming that women had a higher ending Trec and HR (using this to support heat intolerance), does not fully contextualize the use of the IDF HTT, which these two studies used. the IDF HTT uses a fixed intensity as its protocol, meaning that the overall relative intensit(the primary driver for metabolic heat production) is greater in women than men. This is most likely the reason why the differences in failure rates exist....women are required to perform exercise at a greater relative intensity then men, thus producing more body heat.

We have revised the discussion section and discussed only the differences in the heat tolerance test outcomes for males and females. We have excluded the information on the physiological response from the manuscript.

Please see line 271 – 279

Heat tolerance in women and men

Three studies compared heat tolerance classification in males and females using the most commonly used test, the HTT developed by the Israeli Defence Force (Table 3). [12, 27, 28] Druyan et al. investigated gender differences in Israeli Defence Force personnel who had sustained heat injury. The study reported that 67% of the women were found to be heat intolerant compared to 26% of their male counterparts.[12] In the studies conducted by Lisman et al. and Kazman et al. the study population comprised of participants from the university and military communities who had either no heat illness or a previous history of heat illness. Both studies reported that a greater proportion of women were classified as heat intolerant compared to men (42% vs 27% and 45% vs 18% respectively). [27, 28]

4) Within the discussion, the authors aim to discuss the differences in heat illnesses in women compared to men. The discussion on lines 354-355 as well as the supporting discussion below (L356-364) is inherently flawed. The specific occupations within the Armed forces in which women and men have are different. Until recently (within the last 1-2 years), women have been prevented from serving in certain roles (infantry, special operations, etc.), and given the demands of these specific job roles, men would have a higher EHS rate.

Using more current literature, indicating that service members engaged in combat roles have an increased risk of exertional heat illness we have revised the discussion and included the information about how gender exclusion from specialized military roles may account for the higher heat stroke incidence rates in males.

See lines 325 – 339

Incidence and prevalence of exertional heat illnesses in women compared to men

In this review, women had a lower incidence of heat stroke, but a slightly higher incidence of other heat illness compared to men. The reported lower incidence of heat stroke/higher incidence of other heat illness in women compared to men could possibly be due to the fact that women in the military in the United States were excluded from combat positions until 2013 when the ban was lifted.[20] Evidence in the literature suggests that service members who were engaged in roles such as infantry or gun crew had an increased risk of heat illness, possibly reflecting a greater risk of heat illness for those in combat roles.[34] Furthermore, during military training exercises men may have comparatively tolerated working in the heat beyond the endurance limits.[22] This finding was re-echoed in a previous systematic review that men in the general population had a higher rate of all types of heat illnesses compared to women.[21] Although, the incidence of heat stroke was lower in women compared to men in this review, the incidence of heat stroke among women has increased over the past four years. This implies that as more women engage in specialised military roles their risk of exertional heat illness increases.

Furthermore, the discussion on Lines 365-370 is not fully representative of the published literature on this topic. Early literature examining thermoregulatory differences between men and women have shown that the sweating responses and cutaneous vasodilation responses were primarily responsible for differences in thermoregulation. Contemporary literature has shown that differences in thermoregulation across the menstrual cycle are subtle and are nullified when factoring in the extent of environmental stress and/or behavioral responses. It must be further noted, that there are limitations in interpreting some of this literature (controlled laboratory studies) into field-based settings as the results between these two studies are conflicting.

We have revised the manuscript and included more recent research highlighting the effect of humidity on exercise and heat loss during menstrual cycle phases.

Please see lines 349 – 350

However, conflicting evidence suggests that in highly trained women, exercise performance and heat loss is not affected by the menstrual cycle phase but is impaired in humid conditions.[51]

Please see lines 404 – 406

Given that the heat tolerance test was conducted in a laboratory setting, more research is needed to replicate the findings in field based setting.

5) L376-425 discuss risk factors regarding heat illness, however, these are not specific to gender, the purpose of this study.

We have revised the manuscript to reflect only gender specific risk factors.

Please see lines 340 – 360

Gender specific risk factors for heat illness

Despite the lower incidence of heat stroke, women had a greater risk of exertional heat illnesses compared to men.[30, 33] In addition one study attempted to investigate intra gender risk factors for exertional heat illness.[49] Slower run time duration was associated with exertional heat illness among males and females respectively, while higher BMI was identified as a risk factor among males only.[49] The higher risk of exertional heat illnesses in women may likely be due to differences in physiological and physical characteristics between men and women.[50] Physiological characteristics such as hormones, use of contraceptive pills and lower evaporative heat loss may make women more susceptible to heat illness. [11, 13] However, conflicting evidence suggest that in highly trained women, exercise performance and heat loss is not affected by the menstrual cycle phase but is impaired in humid conditions.[51] In addition, physical characteristics such as lower aerobic fitness is a predictor of exertional heat illness.[50] Generally, women have lower aerobic fitness levels and lower overall work capacity which may contribute to the increased risk of exertional heat illness.[50] Individuals with low aerobic fitness levels are likely to exert themselves beyond their physical limit and are at increased risk of heat illness.[52] Other intra gender risk factors that were identified were slower/longer run time duration and higher BMI.[49] Evidence suggests that slower run time duration which may be a reflection of lower aerobic fitness and higher BMI increases the risk of heat illness.[49, 53] However, the evidence is limited given that this was reported by only one study.[49]

Reviewer: 3

Reviewer Name

Dr. Sharoon Hanook

Institution and Country

Forman Christian College (A Chartered University) Lahore Pakistan

Please state any competing interests or state ‘None declared’:

None Declared

Please leave your comments for the authors below

We thank the reviewer for his comments. We carefully considered the feedback and addressed the comments below. Concerning the meta-analysis, we initially did not conduct one because we considered the included studies as heterogonous. However, while addressing previous reviewer feedback, we interpreted a comment on the statistical analysis as a request to conduct a meta-analysis. Based on the current concerns raised by the reviewer, we have excluded the meta-analysis from the review.

1. I wonder if the researcher has studied the agreement among the various reported studies.

We acknowledge that the studies included in the review are heterogonous and we therefore initially did not conduct a meta-analysis. The meta-analysis was included based on our interpretation of previous comments from one of the other reviewers. Currently, the manuscript has been revised and the meta-analysis has been removed.

2. I am unable to understand the point of having table 2 and table 3, this does not answer the research question. A lot of tables should be either omitted or reorganized to bring more consistency and clarity in reporting arguments.

Given the gender differences between males and females, women in the armed forces are at an increased risk of experiencing heat illness. It is important to highlight the risk factors and gender differences in heat tolerance. Furthermore, if they are subjected to the heat tolerance test as part of the return to duty process, they may be at a disadvantage given that the protocol was developed among male participants. We understand that the economic burden as well as the defence operational implications of heat illness is significant. If a female participant is considered heat intolerant, the operational implications as well as career implications for the participant may be negative.

We have made the justification for the inclusion of Table 2 and Table 3 which address risk factors and heat tolerance in the introduction.

Please see lines 97– 125

Among armed forces personnel exertional heat illness continues to pose as a significant cause of morbidity and mortality [7]. Operations and training may involve exposure to high ambient temperature and high workload which may result in heat illness.[7] Historically, men have occupied military roles and responsibilities with fewer proportion of women in the armed forces.[8] However, increasing numbers of women are joining the armed forces globally following the inclusive approach to recruiting and creation of more roles for women.[9] Women are required to operate in austere environments with heat illnesses becoming more frequent.[9] This has raised the question about gender differences in thermoregulation during heat stress.[9] Evidence suggests that women differ from men in thermal responses to heat.[10] This difference may be because women have a lower rate of whole body evaporative heat loss, higher body fat mass, body mass ratio,[11] number of sweat glands and lower aerobic fitness.[12] In addition, hormonal variations due to menstrual cyclic patterns and the use of contraceptive pills may be associated with the differences in response to heat stress.[13]

When exertional heat illness occurs, it may be challenging to determine if an individual may return to duty. An inaccurate determination of complete recovery among armed forces personnel may negatively impact military readiness.[14] While, there are no evidence-based recommendations for return to duty, the American College of Sports Medicine (ACSM) guidelines states that exertional heat stroke patients may return to duty after re-establishing heat tolerance.[15] However, individuals vary in their ability to cope with heat stress and the inability to withstand heat stress during exertion in hot environments is defined as heat intolerance.[2] Evidence suggests that heat intolerance may be as a direct result of heat stroke or due to predisposing inherent factors (genetics).[2] However, the objective criteria or measure for defining heat tolerance or intolerance remains a subject of controversy.[14] The current return to duty guidelines for military personnel varies across countries.[16] For example, in the United States, military return to duty process is based on clinical assessments with gradual acclimatization and re-introduction of duties.[17] By contrast, return to duty in the Israeli Defence Force requires a heat tolerance test to determine if an individual is heat tolerant.[18] Therefore, it is important to develop evidence based return to duty protocols across the globe.

3. In the PRISMA Checklist authors says Subgroup analysis to be "NA" but in line 213 it is discussed and reported in supplementary figure 1. Moreover, in the subgroup analysis both the categories are not mutually exclusive, as Heat exhaustion is considered in both the factors used to carry out subgroup analysis, wondering if there was any duplication of the data? Please clarify?

We have revised the manuscript based on the reviewers' concerns and excluded the meta-analysis.

4. Subgroup analysis in Figure 3 shows moderate to high heterogeneity among the studies. Researchers need to consider this while concluding the research.

We have revised the manuscript based on the reviewers' concerns and excluded the meta-analysis.

5. Supplementary Table 3 shows zero QATSDD scores for three studies and very low score for many for the many studies, if there was no relevance of these studies with the objectives and other aspects of the study then shouldn't these studies be excluded from the Meta-Analysis.

We have excluded the three studies from the review.

Please see Supplemental Table 5

6. Please check why in the overall analysis the Risk Ratios (figure 2) favors women but in the subgroup analysis (figure 3) risk ratios favor men?

We have revised the manuscript based on the reviewers' concerns and excluded the meta-analysis. Therefore, there are no figures related to the meta-analysis included in the review.

7. There should be more clarity that how the data were categorized into various categorize described in lines 195 – 206.

We have revised the methods section and redefined the categories.

Please see lines 208 - 219

Data analysis and synthesis

In this review, the International Classification of Diseases ICD 9 or ICD 10 diagnosis codes [25, 26] for the effects of heat and light were used to classify heat illnesses. All included studies utilized either the ICD 9 or ICD 10 codes to classify heat illnesses depending on the year of publication. Heat illnesses were categorised as heat stroke and other heat illnesses (including heat exhaustion and unspecified effects of heat and light). Heat stroke was identified and defined using the ICD diagnosis codes 992.0 (1CD 9) and T67.0 (ICD 10). While other heat illnesses were defined as heat exhaustion (992.3-5, T67 3-5) and unspecified effects of heat and light (992.9 and T67.9). In addition, some studies presented findings for all heat illness without categorizing them into heat stroke and other heat illnesses. These findings were presented separately. Incidence rates and proportions were extracted from the data reported in each study and used for the analysis in this review.

8. The figure at Page 49, has no information that why it has been reported, I also present subgroup analysis that is reported in Figure 3

We have revised the manuscript based on the reviewers’ concerns and excluded the meta-analysis.

8. I agree with the comments of the other reviewer that states.

"Within the Data Analysis and Synthesis section, the authors classification of heat illnesses present an issue. The categorization was heat illness, heat stroke, and other heat illnesses. The categorization of the conditions representative of the heat stroke and other heat illness categories are also embedded within the heat illness category, thus this data is counted twice. It is strongly suggested that categorizing as either heat stroke or other heat illnesses is the most appropriate, particularly how "other heat illnesses" are assessed within the Armed Forces, and the changes in classification that have occurred in the Armed Forces in the "other" category in the last 5 reporting years (US Armed Forces data, which is included in this study). Furthermore, on Line 209, the authors state that risk factors related to heat illnesses were not pooled, however, on Line 212, the authors state that this data was pooled, and the data presented in the results shows pooled data."

We have revised the methods section and redefined the categories.

Please see response above (lines 208 – 219).