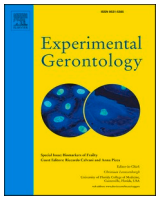
Experimental Gerontology 206 (2025) 112777

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero



Review article

Heat stress effects on the immune system of older adults: A systematic literature review

Rabab Awad [a,*], Assaf Suberry [a], Ahmad Abu-Akel [b,c], Liat Ayalon [a]

[a] Louis and Gabi Weisfeld School of Social Work, Bar Ilan University, Ramat Gan, Israel
[b] School of Psychological Sciences, University of Haifa, Haifa, Israel
[c] The Haifa Brain and Behavior Hub (HBBH), University of Haifa, Haifa, Israel

ARTICLE INFO

Section Editor: Michael Drey

Keywords:
Heat stress
Temperature
Immune function
Aging
Systematic review

ABSTRACT

Objectives: We examined the evidence from experimental and cohort studies concerning the associations between heat stress and immune vulnerability in older adults.
Research design and methods: A systematic search was performed in 6 academic databases, covering all papers that were published until April 2024. We included studies that explored immune-related outcomes associated with climate change, mainly heat shock, heat exposure, extreme temperature and global warming, among older adults, aged 65 and over. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews were followed to select the studies. Records that retained the exact same search terms from databases were imported into COVIDENCE software and were screened by two independent raters. Major findings were identified and synthesised.
Results: Fifteen papers were considered eligible for full-text evaluation, and 4 papers met the inclusion criteria and were included in the analysis. Studies mainly point to age-related dysregulation in heat induced response of subgroups of interleukins and heat shock proteins (hsps).
Discussion and implications: Heat stress may directly affect the regulatory function of older adults' immune system that plays a critical rule in the course of infections and inflammatory diseases. However, this review points to a paucity of relevant studies among older adults.

1. Introduction

Climate change, especially global warming, represents the biggest global health threat of the 21st century and has become an urgent risk factor for mortality and morbidity (Beyeler and Salas, 2022; Cianconi et al., 2020; Field and Barros, 2014; Kotcher et al., 2021; Patz and Olson, 2006). The literature presents various studies about the effects of climate change on the immune systems of various organisms (Caroprese et al., 2021), and points to the effect of heat stress on immunity, affecting several processes such as reproduction, mechanisms of survival, pathogenicity, host–parasite interactions, and disease resistance (Adamo and Lovett, 2011; Burek et al., 2008; Perry, 2017).

In humans and animals, the immune system becomes more fragile with aging, this occurs due to gradual and cumulative alterations and impairments of various types of immune cells, leading to phenomena like "Immunosenescence" and "Inflamm-aging" (Day, 2010; Mälzer et al., 2016). These phenomena describe age-related vulnerability of the immune response to environmental challenges, resulting in decreased vaccination efficiencies, and more frequent incidence of infections and diseases.

The deregulated immune function with aging, may be attributed to its interrelation with the central nervous system, sharing mediators/neurotransmitters and synapses for mutual communications (Daëron, 2022; Mapunda et al., 2022). Specifically, age-related changes in the hypothalamus–pituitary–adrenal (HPA) axis plays a critical role in the regulation of the immune system in exposure to stressful triggers (Buford and Willoughby, 2008), and can lead to alteration in a variety of immunologic, metabolic, and cognitive processes (Chojnowska et al., 2021; Hawkley and Cacioppo, 2004).

The immune system functioning can be monitored by a different biomarkers that participate in biological and physiological processes. This can be done by detecting *the levels of cortisol and dehydroepiandrosterone (DHEA)— neurohormones that regulate the immune system functioning, in the blood or saliva—, by detecting immune parameters like the*

* Corresponding author.
E-mail addresses: awadrabab@gmail.com (R. Awad), aabuakel@psy.haifa.ac.il (A. Abu-Akel), liat.ayalon@biu.ac.il (L. Ayalon).

https://doi.org/10.1016/j.exger.2025.112777
Received 5 March 2025; Received in revised form 11 April 2025; Accepted 5 May 2025
Available online 6 May 2025

secretory immunoglobulin A (S-IgA), or by detecting interleukins that are secreted in response to different types of stressors (Buford and Willoughby, 2008; Chojnowska et al., 2021; Hawkley and Cacioppo, 2004; Bauer, 2005; Kamin and Kertes, 2017). Each type of these biomarkers is sensitive to specific pathophysiological aspects of a particular stress (Dhama et al., 2019). *Accordingly, measuring the effects of heat stress on the immune system among older* adults can be conducted by examining the relevant biomarkers.

Research has shown alteration in some immunological parameters in response to heat stress exposure (Jafari et al., 2020a; Starkie et al., 2005a, 2005b). For example, analyses of blood samples revealed a significant decrease in white blood cell count and lymphocyte levels, and pointed to a significant increase in neutrophil and IgM levels in heat exposure of 32.97 ± 3.22 °C, suggesting that heat stress may weaken and suppress the human immune system[20]. In another study, circulating levels of both *interleukin-6* (IL-6*)* and tumor necrosis factor alpha (TNFα) were elevated in heat exposure of 35 °C (Starkie et al., 2005a, 2005b).

Older adults are particularly vulnerable to environmental heat exposures, and experience significantly greater adverse heat-related health outcomes, mainly due to aged-related impaired thermoregulatory control and reduced physiological adaptability (Balmain et al., 2018; Leyk et al., 2019), alongside age-related compromised immune system, causing heat-induced inflammations and illnesses (Buford and Willoughby, 2008; Hawkley and Cacioppo, 2004; Millyard et al., 2020; Phillips et al., 2007).

The present review aimed to provide a state-of-the-art summary of the potential effects of heat stress on the immune system of older adults, aged 65 and over, and associated health consequences of these effects. The review was guided by the following questions: a) What are the effects of heat stress on the immune system among older adults? b) What are the factors known to affect these associations such as type of heat exposure and period of time of heat exposure? c) What immune biomarkers are sensitive to heat stress among older adults?. This systematic review thus aims to point to the impact of heat stress on older persons' immune system in order to guide further research and interventions to possibly reduce or ameliorate the negative impact of heat stress on older adults.

2. Method

2.1. Search strategy and study selection

The search was conducted across 6 academic electronic databases: PubMed, PsycINFO, Embase, Cochrane Database of Systematic Reviews, PsycArticles, and Scopus. No starting restrictions were applied; we included all studies conducted up until April 2024. Key-word search included terms related to heat stress (climate change, climate impact, climate outcome, climate effect, heat, heat waves, heat exposure, temperature, global warming), and immune-related key concepts (immune, immunological, immune system, immune function, immune response), that refer to older age (aged, aging, old, old age, older adults, elderly). A specific search string was developed with a librarian for PubMed (see eAppendix A in the Supplement) and was modified according to the specific search requirements of each of the databases, while retaining the exact same search terms. The results were entered into the Covidence software programme for systematic reviews (Covidence, 2024). In addition, two reviewers (RA and LA) manually screened reference lists of included records and systematic reviews regarding climate change and heat stress, employing snowballing technique to identify additional relevant research. Duplicates were deleted, and irrelevant results were removed. The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We registered our protocol PROSPERO (ID: CRD42024519482). Title and abstract, and full-text review was performed independently by two raters (RA and AS), who resolved disagreements through consensus with a third reviewer (LA).

2.2. Eligibility criteria

The eligible criteria for our research questions were guided by the "PECO" framework as the follow: P (humans aged 65 and over), E (heat stress), C (*nonexposed* older humans or exposed young humans), and O (dysregulations in immune biomarkers and their implications on health). Table 1 summarizes the Inclusion/exclusion criteria.

2.3. Inclusion and exclusion criteria

The following inclusion criteria were used to guide the search for relevant articles: a) peer reviewed, b) written in English, c) randomized controlled trials, cohort studies, longitudinal designs, single-case studies, pre/post designs, case-control designs, cross-sectional designs, Studies were excluded if they were: a) non-human studies, b) conference proceedings, study protocols, and studies validating data collection tools, c) reviews, d) theses and doctoral dissertations, e) chapters from books, f) policy-level intervention studies, and g) literature reviews, meta-analyses, theoretical or methodological papers, and h) studies with non-available abstract and full-text in English. Excluded title, abstract or full-text records were documented to keep track of justification for exclusions.

2.4. Strategy for data synthesis: Collating, summarizing, and reporting the results

Eligible studies were presented using summary tables in structured forms and categories, taking into account characteristics of the studies such as authors and year of publication, characteristics of participants, including gender, age groups, location\region, heat exposure, biomarkers of the immune system, measurement techniques, main findings, study type. Quality assessment was guided by the Agency for Healthcare Research and Quality (AHRQ) methodology checklist (Rostom et al., 2004).

3. Results

3.1. Literature search

The search strategy was conducted between March 1, 2024 and July 31, 2024, yielded 1480 articles (861 Cochrane, 220 Web of Science, 63 Scopus, 0 PubMed, 0 APA PsychNet, 0 Embase, and 30 snowballing \hand searching). After removing 308 duplicates, 1172 articles were maintained. 1157 were excluded based on title and abstract screening. Fifteen papers were moved to full-text review and 4 studies that met the

Table 1
Inclusion/exclusion criteria of "PECO" strategy for the systematic review of the effect of heat stress on immune system.

Criteria	Include	Exclude
P (patient/ population/ problem)	In vivo and in vitro experiments\ tests that sampled immune biomarkers of humans (aged 65+), from blood, urine or any source from the body.	Microorganisms, animals, humans with cancers, and with a history of heat-related illnesses or conditions affecting thermoregulation (heat stroke, dehydration, thyroid disorders), or with pre-existing medical conditions that can mask the effect of heat stress.
E(exposure)	Laboratory heating, climate- related heat exposure.	Body heating that was related to treatment or other physical intervention.
C (comparison/ control)	Control group of *nonexposed* participants, or comparison with group of exposed young participants.	Control group of animals
O (outcome)	Alterations in immune biomarkers levels	Cells carcinoma, tumors.

criteria were chosen for data extraction. Fig. 1 presents the search flow, using the PRISMA guidelines.

3.2. Characteristics of included studies

In One study, it was clearly stated that it was a randomized study, and one as cross-sectional (Jurivich et al., 2005), the 2 other had no indication of the study type. Two studies were (*pre–post*) *studies (*Baranauskiene et al., 2023*;* Foster et al., 2023). Two articles originated in and focused on the United States, the others in Lithuania and Australia. The earliest article identified was written in 1999 (Rao et al., 1999), one in 2005 (Jurivich et al., 2005), and other 2 were conducted in 2023 (Baranauskiene et al., 2023*;* Foster et al., 2023) (see Table 2 for study characteristics). All studies used "In vitro" sampling for examining immune cells after heat exposure, in two it was also accompanied by "In vivo" measurements (Baranauskiene et al., 2023*;* Foster et al., 2023). Blood samples were taken to extract and detect immune biomarkers with different assays, comparing between young (16-40y) and older participants ((+65. Two studies exposed immune cells to heat stress and the other two used body heating, one used bath water at 43 °C (HWI-43 °C) for a 5-min exposure (Baranauskiene et al., 2023*)*, and in the other study, participants entered the environmental chamber set to the desired temperature of 47 °C (46.3 ± 0.6 °C), for a 3-h heat exposure with suitable instrumentation and vital signs were monitored continuously (Foster et al., 2023).

Participants in one study were younger and older males (Baranauskiene et al., 2023*)*, two study included men and women (8 males, 8 females from each age- group) (Foster et al., 2023), and other study consisted of 67 % men and 33 % women (Jurivich et al., 2005). The fourth study had no reference to gender (Rao et al., 1999). All studies sampled lymphocytes to examine different parameters of the immune system, targeting different types of interleukins in two studies (Baranauskiene et al., 2023*;* Foster et al., 2023), heat shock proteins (Jurivich et al., 2005), and in two studied included biomarkers with immunomodulatory and immunoregulatory properties such as prolactin, cortisol and dopamine (Baranauskiene et al., 2023*)*, intestinal fatty acid binding protein (I-FABP) a plasma marker of intestinal injury and inflammation (Lau et al., 2016) and tissue factor (TFlog) that one of its roles includes signaling activity which promotes pleiotropic inflammatory responses (Witkowski et al., 2016). Table 2 presents the characteristics of included studies.

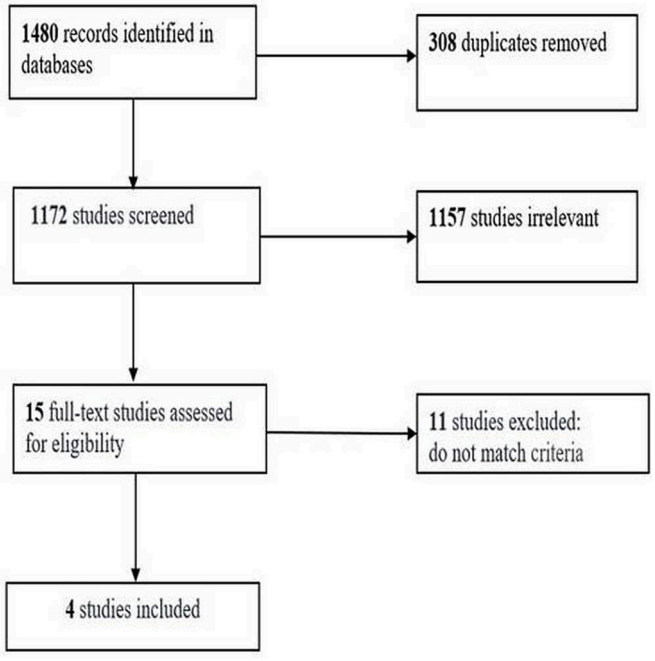


Fig. 1. PRISMA flow of research articles.

3.3. Quality assessment

The quality evaluation of eligible articles was performed using the Agency for Healthcare Research and Quality (AHRQ) checklist as was applied in similar study (Zhou et al., 2023). The quality of the literature was assessed by the percentage of "yes" answers)"Yes" answers divided by the sum of all the answers), where <30 % was considered low quality, 30 %–60 % medium quality, and > 60 % high quality (Rostom et al., 2004). Due to the type of the design of the studies, some of items in the ARHQ Methodology Checklist were not applicable, in three studies it was not applicable to evaluate the follow-up and the percentage of patients for which incomplete data or follow-up was obtained, and were handled as 10 items (Jurivich et al., 2005; Baranauskiene et al., 2023; Rao et al., 1999), and in one of these studies, there was no explanation of any patient exclusions from analysis, and was handled as 9 items (Jurivich et al., 2005). Two study met the criterion for high quality (64 %, Foster et al., 2023; 70 %, Baranauskiene et al., 2023); one for medium quality (55 %, Jurivich et al., 2005), and one for low quality (30 %, Rao et al., 1999). See Table 3.

3.4. Descriptive analysis of the main findings

Our systematic review identified 4 relevant studies that were eligible for data extraction. The main findings of the studies showed that exposure of heat stress induce age-related dysregulation in immune biomarkers, where most of these changes, in comparison with younger participants, were statistically significant. For example, hsp70 and HSF1–DNA binding and gene expression were significantly altered and reduced by age during thermal stress of 42 °C heat shock for 30 min, while no statistically relevant differences were noted regrading heat shocked HSF1 and HSF2 protein (Jurivich et al., 2005); notably, exposure to heat stress for longer periods of time (namely, 45, 60 and 90 min) did not manifest in higher levels of HSF1–DNA binding than the levels observed for the 30 min exposure. In one study (Rao et al., 1999), age-related up-regulation in heat induced response was observed for hsp 70, hsp 90, hsp 60, down-regulation in hsps 105, 56, 47, 40, 27, and 16 comparing to younger donors, albeit these differences were dependent on time of exposure (2 h, 3 h, 4 h) and type of hsp. For example, regarding hsp 90 and 105, age differences became more significant when time of exposure was longer. Studies that targeted interleukins to examine the effect of heat stress on immunity, revealed that IL-6 increased more significantly in older men than younger men (Baranauskiene et al., 2023), while a significantly decrease was observed in IL-8 from pre- to post-heat exposure, comparing them to younger males (Foster et al., 2023).

Studies that included a biomarkers with immunomodulatory and immunoregulatory factors also pointed to age-induced dysregulation. In older adults, I-FABPlog significantly increased from pre- to post-heat exposure of 3 h, with no change in young adults (Foster et al., 2023). In the same study, TFlog did not change from pre- to post-heat exposure. In response to hyperthermia (Baranauskiene et al., 2023), cortisol levels increased significantly more in older males, peripheral dopamine levels significantly decreased in older males and increased in young males, and prolactin increased significantly more in young males compared to older males (Baranauskiene et al., 2023).

Interestingly, there was no reference to gender differences in the effects of heat stress on immune biomarkers, although, 2 studies mentioned the number of men and women in the study (Jurivich et al., 2005; Foster et al., 2023).

Based on these findings, we examined the effects of changes in immune biomarkers, as summarized in Table 4. These effects were derived from previous studies addressing the health implications of biomarker dysregulation.

Table 2
Characteristics of studies included.

Author and year of publication	Location	Characteristics of participants	heat exposure protocol	Sample	Biomarker of immune system	Technique	Main Findings
Baranauskiene et al. (2023)[28]	Lithuania.	12 young subjects 19–21 y) and 11 older males (65–80 y) males. Not physically active; right-leg dominant, nonsmokers; not take medication affecting thermoregulation, did not participated in temperature manipulation within the past 3 months, no significant knee injury, surgery or pain.	The study comprised a randomized control trial under a thermoneutral condition at an ambient temperature of 23 °C, 50 % relative humidity and an experimental trial with passive lower body heating in 43 °C water (HWI-43 °C). 5 min' of exposure time was required to achieve desired rectal temperature.	In vivo (Exercise: 2-min MVC[3] task and physiological measurements: Anthropometric and sweating rate Measurements, heart rate, body temperature, and thermal sensation measurements) & in vitro (Pre and post heat exposure venous blood samples).	Prolactin, interleukin-6, cortisol & dopamine.	Enzyme-linked immunosorbent assay (ELISA) (prolactin and IL-6) Dopamine ELISA AIA-2000:automated enzyme immunoassay analyzer (cortisol)	Prolactin increased more in response to hyperthermia in young males, interleukin-6 and cortisol levels increased more in older males. Dopamine levels decreased in older males and increased in young males in response to hyperthermia.
Foster et al. (2023)[29]	USA.	16 young subjects: 8 males, 8 females (21-39y), & 16 older subjects: 8 males, 8 females (65-76y).not diagnosed with gastrointestinal diseases, with normal heart rate.	A 3-h exposure to very hot and dry (47 °C, 15 % humidity) heat.	In vivo (Intermittent activity at 3 METS, and physiological measurements), and in vitro. Pre and post heat exposure venous blood samples.	I-FABPlog[4], interleukin-8 (IL-8log), & tissue factor (TFlog).	Enzyme-linked immunosorbent assay (ELISA).	Increase in I-FABPlog concentration (an index of enterocyte damage) in older humans during a 3-h extreme heat exposure. TFlog decreased in the younger group, and observed decrease in IL-8log in the older group (No change in these markers in the other cohort).
Jurivich et al. (2005)[27]	USA.	27 young donors (20-40y) & 37 older donors, aged 70+. Good self-reported health, not taking immunosuppressive medications.	T-cells were exposed to a transient heat shock of 42 °C in circulating water bath for 30 min'.	In vitro. Blood samples	Lymphocytes (T-cells): hsp gene, HSF[2] (protein)–DNA binding	Eectromobility shift assays (EMSA). Electrochemiluminescence. Nuclear run-on assays.	Nuclear run-on analysis revealed a 66 % reduction in hsp70 transcription rates in T-cell nuclei from older donors compared to those from younger donors, and a 47 % reduction in HSF1–DNA binding was observed in T-cells from older donors relative to those from younger donors
Rao et al. (1999)[30]	Australia	8 young subjects (16-29y) and 4 older subjects (76-84y). healthy, not taking prescribed or non-prescribed medication.	Heat shock from 37 to 42 °C for 60 min` in an incubator under 5 % Co2 and 95 % humidity, and then allowed to recover at 37 °C for various times.	In vitro. Blood samples.	Lymphocytes: heat shock proteins[5]	Polyacrylamide gel electrophoresis, autoradiography analyses, immunoblotting, western blot analysis, de novo protein synthesis.	Age-related dysregulation in heat induced response of hsp 70, hsp 90, hsp 60 (up-regulation), hsps 105, 56, 47, 40, 27, and 16 (diminution), down-regulated proteins at 100, 38, and 18 kDa.

Note: [1]AHRQ's assessment methodology, [2] Heat shock transcription factor, [3]Maximal voluntary contraction, [4] Intestinal fatty acid binding protein. [5] hsps proteins are classified based on their molecular weights, mainly including large hsps, hsp90, hsp70, hsp60, hsp40, and small hsps.

Table 3
Quality assessment of the included studies using the Agency for Healthcare Research and Quality (AHRQ) checklist.

No.	Item	Baranauskiene et al. (2023)[28]	Foster et al. (2023)[29]	Jurivich et al. (2005)[27]	Rao et al. (1999)[30]
1	Define source of information (survey, record review).	Y	Y	Y	Y
2	List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications.	Y	Y	Y	N
3	Indicate time period used for identifying patients.	N	N	N	N
4	Indicate whether or not subjects were consecutive if not population-based.	Y	Y	N	N
5	Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants.	N	N	N	N
6	Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements).	Y	Y	Y	Y
7	Explain any patient exclusions from analysis.	Y	Y	NA	N
8	Describe how confounding was assessed and/or controlled.	N	N	N	N
9	If applicable, explain how missing data were handled in the analysis.	Y	Y	Y	N
10	Summarize patient response rates and completeness of data collection.	Y	Y	Y	Y
11	Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained.	NA	Y	NA	NA
	ARHQ* score	7/10 (70 %)	7/11 (64 %)	5/9(55 %)	3/10 (30 %)

Note: Yes = Y;, No = N; Unclear = U; Not applicable = NA.
* ARHQ Methodology Checklist for cross-sectional study (http://www.ncbi.nlm.nih.gov/books/NBK35156/).

Exposing older adults to heat stress resulted in changes in hsps, primarily hsp70, hsp60, and hsp90. These heat shock proteins play major role in the metabolic process of proteins at the cellular level, processing of proteins antigens, and have a protective role in response to stressors (Hu et al., 2022), which explains their associations with various illnesses and diseases, as outlined in Table 4. For example, older adults exhibited low levels of hsp70 in exposure to heat stress. The consequences of such a change in this type of hsps can lead to several health conditions such as insulin resistance and metabolic risk factors such as high BMI, increased waist circumference, and increase in body fat percentage (Islam et al., 2014), as well as health conditions like obstructive sleep apnea, arteriosclerosis, fatty liver disease, and cardiovascular disorders (Qu et al., 2015).

Heat-induced changes were also observed the levels of interleukins. For instance, an increase in IL-6 levels was evident in both younger and older adults, but it was significant in older adults. Elevated levels of this biomarker has been linked to infectious diseases (Al-Qahtani et al., 2024; Eichberger et al., 2022), and can serve as a useful marker for peripheral inflammation, especially in older adults (Tylutka et al., 2024). In contrast to the increase in IL-6 levels, IL-8 levels were significantly lower in older adults compared to younger adults. Low levels of IL-8 have been documented in previous studies, and have been linked to inflammatory reactions (Harada et al., 1994), and psychiatric disorders (Tsai, 2021).

Exposure to heat stress can also induce age-related changes in immunomodulatory factors such as cortisol, dopamine, and I-FABPlog (see Table 4), which may contribute to immune dysregulation, resulting in several inflammatory and neurodegenerative diseases (Amiri-Dashatan et al., 2022; Kamin and Kertes, 2017; Phillips et al., 2007; Zheng et al., 2020).

As shown in Table 4, prolactin is another heat-sensitive immunomodulatory factor; high levels of this biomarker have been associated with health outcomes like defects in cognitive abilities and psychotic disorders (Labad, 2019; Studerus et al., 2021).

Furthermore, heat stress has been shown to impact gene-level processes in older adults, by altering the levels of HSF1–DNA binding, a transcription factor for hsps, leading to impairments in hsps expression and increased vulnerability to neurodegenerative diseases (Liu et al., 2022).

In summary, heat-induced abnormalities in immunomodulatory factors and immune biomarkers may contribute to a wide range of health outcomes among older adults. For detailed findings, refer to Table 4.

4. Discussion

Our systematic review aimed to identify available literature that addressed the effects of heat stress on the immune system among older adults. Four studies matched the review criteria. All studies in this review supported age-dependent dysregulation in immune biomarkers compared with younger participants, when exposed to heat stress. Our review identified that blood samples that were subjected to body heating or laboratory heating, resulted in abnormality in T lymphocytes components regulation, mainly in heat shock proteins (hsps) functioning, reduction in hsp70 transcription rates and HSF1–DNA binding levels, decrease in IL-8log and dopamine levels, and increase in levels of several biomarkers such as IL-6 levels, I-FABPlog concentration and cortisol levels.

We found that heat stress triggers the immune response depending on the type of heat exposure or period of time of heat exposure. All studies applied heating at or above 42 °C to induce severe hyperthermal body conditions, which acted as a sufficient stressor to elevate peripheral neurohormones and immune biomarkers in the blood (Baranauskiene et al., 2023).

The exposure times varied from 5 min to 3 h, depending on the type of heating method used. For example, changes in interleukins and in

Table 4
Summary of changes in immune biomarkers following exposure to heat stress in older adults and their health implications.

Biomarker		Heat exposure	Young adults	Older adults	Potential implications on health
HSPs					
	HSP70	42 °C, 30 min'.			Tumors, Neurodegeneration diseases (Hu et al., 2022; Tsan and Gao, 2009). autoimmune diseases infections, inflammations (Al Meslamani, 2024; Khan and Ghazanfar, 2018; Wu et al., 2016), including malaria, leishmaniasis, tuberculosis and leprosy (Rao et al., 1999).
	HSP90	37–42 °C, 60 min`			
	HSP60				
interleukins					
	IL-6	43 °C,5 min'	1		Infectious diseases (Al-Qahtani et al., 2024; Eichberger et al., 2022)
	IL-8	47 °C, 3-h			Incidence of several diseases, including psychiatric disorders (Tsai, 2021). inflammation reactions (Harada et al., 1994)
Immunomodulatory Factors					
	I-FABPlog	47 °C, 3-h			Enterocyte damage and gastrointestinal tract infections and diseases (Foster et al., 2023; Saia et al., 2021; Weng et al., 2021)
	Cortisol	43 °C, 5 min'	2		Defects in immune regulation, psychological and health diseases and illnesses (Kamin and Kertes, 2017; Phillips et al., 2007) as Alzheimer's disease (AD) (Zheng et al., 2020), acute myocardial infarction (AMI) (Faresjö et al., 2020), and even to severe COVID-19 infection (Amiri-Dashatan et al., 2022).
	Dopamine				Defects in immune regulation, inflammations, Parkinson's disease, metabolic syndrome and obesity, defects in calcium mobilization, anxiety- and inflammatory bowel disease, neurological and neuropsychiatric diseases (Franco et al., 2021; Pirchio et al., 2022)
	Prolactin		3		Defects in cognitive abilities and psychotic disorders (Labad, 2019; Studerus et al., 2021)
Transcription factor for HSPs					
	HSF1–DNA binding	42 °C, 30 min'.			Age-dependent and neuron-specific vulnerability to neurodegenerative diseases (Liu et al., 2022)

Note: = increase, = decrease, = no change. [1]Not significant; [2] increased slightly, not significant; [3] increased less than young adults.

immune-regulating neurohormones, cortisol and dopamine, were demonstrated even at a 5-min exposure to body heating (Baranauskiene et al., 2023), whereas alteration in T-cells (proteins, gene level, and protein–DNA binding) were observed at a 30-min exposure of laboratory heating (Jurivich et al., 2005).

The results have significant implications in the current discourse regarding global warming, and the effects of heat stress on health, especially among the older population. The immune system plays a critical role in regulating inflammation and diseases processes, and as individuals age, it becomes increasingly difficult for the body to adapt to heat stress. One of the indicators of impaired adaptive immune system is the decline in T cells and its receptors' diversity and sensitivity to stimuli (Tansey et al., 2022). The impaired response of hsps to heat stress, such as the reduction in hsp70 transcription rates and HSF1–DNA binding among old nuclei harvested from T-cells, can be a supportive evidence for age-related reduction in response and adaptation to heat stress. Heat shock proteins such as hsp60, hsp70, hsp90, and gp96, play vital roles in antigen presentation and cross-presentation, activation of macrophages, dendritic cells, and lymphocytes. Malfunction or abnormalities in hsps response or their gene transcription rates (Jurivich et al., 2005) can lead to various health conditions, including neurodegeneration diseases (Hu et al., 2022; Tsan and Gao, 2009). Dysregulations in T-cells lymphocytes can disrupt the immune equilibrium that, impairing the body's ability to mount an optimal immune response against climate-related foreign pathogens. This imbalance may lead to increased infections, inflammations, and the onset of various autoimmune diseases (Al Meslamani, 2024; Khan and Ghazanfar, 2018; Wu et al., 2016).

In addition to T-cells, other immune biomarkers are sensitive to heat stress and have also been examined for their role in worsening health under such conditions. For example, two studies (Baranauskiene et al., 2023; Foster et al., 2023) in this review examined the levels of Interleukins. Interleukins, both a pro-inflammatory and anti-inflammatory cytokine signaling molecules, are key participants in the interactive network of lymphoid organs, cells, and humoral factors in the immune system, and play a crucial role in the development of memory T cells, which are essential for long-term immunity and rapid effective response upon re-exposure (Al-Qahtani et al., 2024; Parkin and Cohen, 2001).

Elevated levels in the pro-inflammatory cytokines, IL-6 and IL-8, have been found in various infectious diseases and sepsis (Al-Qahtani et al., 2024; Eichberger et al., 2022). Elevated as opposed to low levels, especially for IL-8, seem to be more commonly reported in relation to the incidence of several diseases, including psychiatric disorders (Tsai, 2021). Moreover, evidence suggest that low levels of IL-8 can confer benefits due to its role in preventing inflammation reactions (Harada et al., 1994). In contrast to the apparent association of elevated levels of IL-8 with pro-inflammatory diseases, Foster et al. (Foster et al., 2023) found that IL-8 levels were decreased in exposure to heat stress. In their study, levels of IL-8 were examined in the context of heat-related gastrointestinal lining damage, taking into account intestinal fatty acid binding protein (I-FABPlog), interleukin-8 (IL-8log), and tissue factor (TFlog) as indices of enterocyte damage, systemic inflammation, and blood coagulation. The authors attributed the decreased levels of IL-8 to the potential osmotic stress induced by administering fluids to the participants throughout the protocol (Foster et al., 2023).

In the study by Baranauskiene et al. (Baranauskiene et al., 2023), IL-6 and cortisol levels were measured, along with peripheral catecholamine dopamine concentrations, which served as a marker for sympathetic system suppression in response to lower body heating in older males. While cortisol levels increased in both younger and older adults, the rise was notably higher in the older group. It was suggested that in response to stress, cortisol is released and interacts with IL-6 in a feedback loop targeting inhibition of further cortisol release. The increase in cortisol and IL-6 levels in older participants may point to the age-related hyperactivation of the hypothalamus–pituitary–adrenal axis that regulates the immune system in exposure to stressors (Buford and Willoughby, 2008; Sudheimer et al., 2014).

An age-related abnormal increase in cortisol levels in response to stressors can disrupt the balance between cortisol and dehydroepiandrosterone (DHEA), otherwise known as the DHEA:cortisol ratio. This imbalance can lead to defects in immune regulation, which consequently can cause a variety of psychological and health diseases and illnesses (Kamin and Kertes, 2017; Phillips et al., 2007), such as

Alzheimer's disease (AD) (Zheng et al., 2020), acute myocardial infarction (AMI) (Faresjö et al., 2020), and even to severe COVID-19 infection (Amiri-Dashatan et al., 2022).

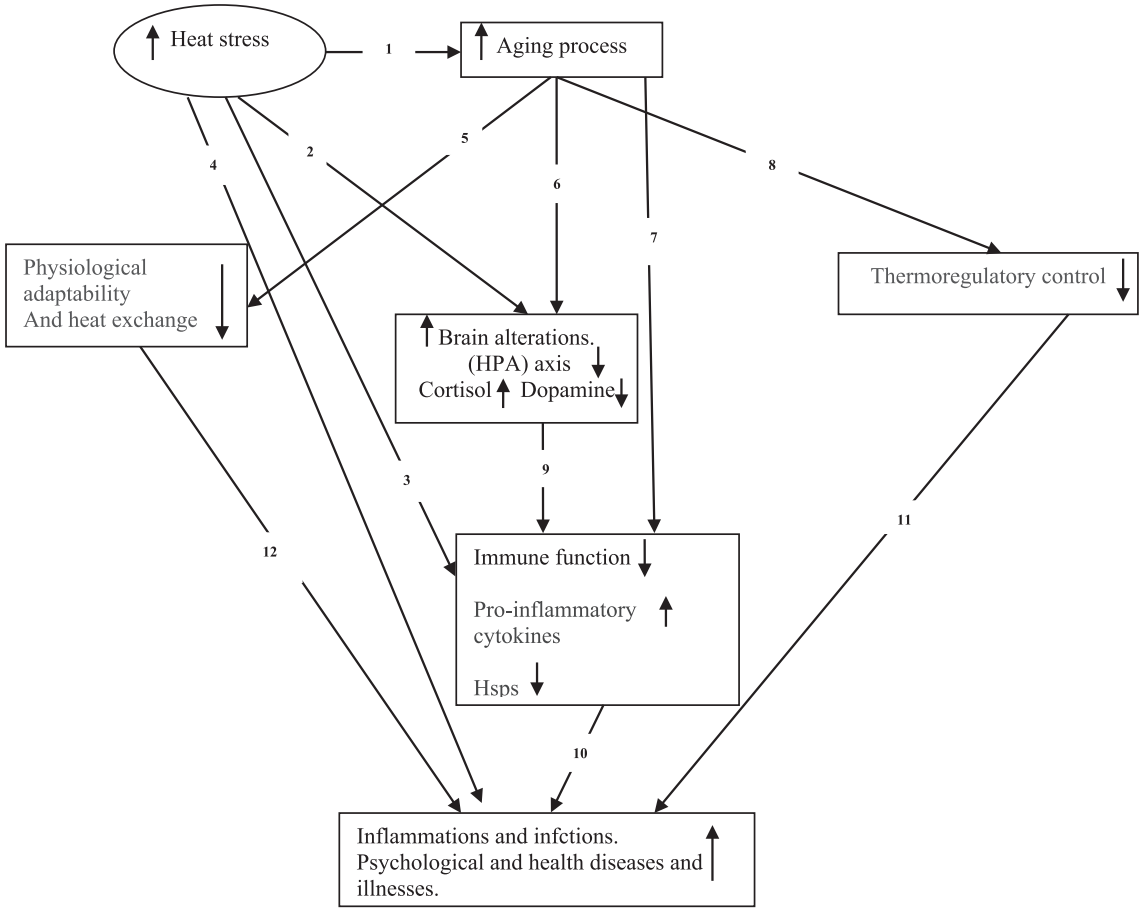
The included studies in our systematic review used different biomarkers such as heat shock proteins, cortisol and interleukins that are sensitive to stress response in order to detect age-related dysregulation in immune response. The reported findings showed consistent age-induced alteration in immune biomarkers in response to severe heat stress of 42 °C and over, with different time exposure depending on type of heating (in vivo vs. in virto). Collectively, these studies emphasize how age-related changes in immune biomarkers are specifically linked to the body's heat stress response, highlighting the need for targeted research into how aging affects the physiological mechanisms underlying heat-induced immune system alterations.

5. Pathways of the potential effects of heat stress on the aging immune system

In Fig. 2, we present a conceptual framework illustrating the likely pathways through which heat stress affects the immune system and, consequently, the health status of older adults. According to the literature presented, heat stress impacts the aging immune system through both direct and indirect pathways, as shown in the studies included in our review (Jurivich et al., 2005; Baranauskiene et al., 2023; Foster et al., 2023; Rao et al., 1999).

Direct pathways primarily represent the direct effects of heat stress on the immune system, involving dysregulation in its function by altering the functions of pro-inflammatory cytokines and heat shock proteins (hsps), as shown in pathways 3 and 10 in Fig. 2.

Indirect pathways include several possible routes. One such pathway (pathway 1) (Adamo and Lovett, 2011; Jafari et al., 2020a, 2020b; Perry, 2017; Starkie et al., 2005a, 2005b; Zannas, 2024) involves the effects of heat stress on the aging process. According to previous literature, environmental factors, particularly heat stress, may challenge the aging process and increase its vulnerability to stressors (Day, 2010; Mälzer et al., 2016); leading to decreased thermoregulatory control (pathways 8 to 11), to reduced physiological adaptabilities in older adults, and may damage their heat exchange abilities (pathways 5 to



[1] Adamo and Lovett, 2011; Jafari et al., 2020; Perry, 2017; Starkie et al., 2005; Zannas, 2024. [2] Butcher and Lord, 2004; Zannas, 2024. [3] Jurivich et al., 2005; Rao et al., 1999; Jafari et al., 2020; Starkie et al., 2005. [4] Al Meslamani, 2024; Wu et al., 2016; Zannas, 2024.[5] Balmain et al., 2018; Buford and Willoughby, 2008; Chojnowska et al., 2021; Daëron, 2022; Hawkley and Cacioppo, 2004; Leyk et al., 2019; Mapunda et al., 2022; Millyard et al., 2020. [6] Butcher and Lord, 2004; Zannas, 2024.[7] Day, 2010; Mälzer et al., 2016 [8] Balmain et al., 2018; Leyk et al., 2019; Millyard et al., 2020. [9] Buford and Willoughby, 2008; Chojnowska et al., 2021; Hawkley and Cacioppo, 2004. [10] Al-Qahtani et al. 2024; Buford and Willoughby, 2008; Eichberger et al., 2022; Millyard et al., 2020; Phillips et al., 2007. [11] Balmain et al., 2018; Jafari et al., 2020; Leyk et al., 2019; Millyard et al., 2020; Starkie et al., 2005. [12] Butcher and Lord, 2004; Millyard et al., 2020, Zannas, 2024.

Fig. 2. Pathways of the potential effect of heat stress on the aging immune system. *Not:* Numbers refer to supportive references for the proposed pathways.

12). These effects combined with the direct impact on immune system function (pathway 7), result in increased inflammation, infections, psychological issues, and other health conditions (pathway 10).

Heat stress can also lead to both direct and indirect alterations in brain function through the hypothalamic-pituitary-adrenal (HPA) axis, as shown in pathways 2 to 9, which represent the direct effects of heat stress on the brain function, resulting in alerted levels of cortisol and dopamine. These neurotransmitters regulate immune system function (Buford and Willoughby, 2008; Chojnowska et al., 2021; Hawkley and Cacioppo, 2004), and dysregulation in their levels may scramble their roles in the body. The pathway from 1 to 6 to 9, represents the indirect effects of heat stress on the brain. Heat stress accelerates the aging process (pathway 1), which leads to the same alterations as seen in pathway 9. These direct and indirect pathways result in varied health outcomes, as seen in pathway 10. Furthermore, heat stress can directly impact the course of various diseases and illnesses, and places a burden on the immune system of older adults, as indicated in pathway 4.

These pathways lead to negative health and mental outcomes (Buford and Willoughby, 2008; Millyard et al., 2020; Phillips et al., 2007; Al-Qahtani et al., 2024; Eichberger et al., 2022), including infections, inflammations, autoimmune diseases (Al Meslamani, 2024; Khan and Ghazanfar, 2018; Wu et al., 2016), neurological and neuropsychiatric diseases (Franco et al., 2021; Pirchio et al., 2022); as well as cognitive impairments and psychotic disorders (Labad, 2019; Studerus et al., 2021). For a detailed list of potential health implications, refer to Table 4.

6. Limitations and future recommendations

Our systematic review has several limitation. First, in the stage of identifying relevant studies by chosen keyword, running the term “heat stress” yielded hundreds of thousands of papers that did not match the specific topic of our review, and mostly included papers addressing “psychological stress”. Therefore, we used different keywords that referred to heat stress and global warming such as “heat”, “heat waves”, “heat exposure”, “temperature “, and “global warming”. We assumed that studies that included the term “heat stress” could be detected using the word “heat” and other keywords regarding global warming. A wide handsearch was conducted by two reviewers (RA and LA) to diminish this bias.

It is important to note that none of the four studies included in the systematic review, which used mechanical heating, addressed the effects of global-warming-related heat stress. Hence, outcomes of these studies and our interpretations of the effects of heat stress on the immune system in older adults in reference to global warming are speculative at best. Future studies should aim to investigate the effects of heat stress on the aging immune system and its health implications by examining populations exposed to natural heat stress by during periods of extreme heatwaves.

Moreover, the samples in all four studies are very small and relied on diverse protocols. It is important to note that the outcomes of studies can be variable depending on parameters such as study design, sample, control group, temperature, relative humidity, and the duration of exposure to heat (Habibi et al., 2022). Comparing outcomes of these studies that differed in time of exposure, type of heating, and immune biomarkers, is not ideal, and might be bias the conclusions that can be drawn. The studies' design and sample size were also reflected in the quality assessment. Two studies (Baranauskiene et al., 2023; Foster et al., 2023) were of high quality and the others were of low to medium quality (Jurivich et al., 2005; Rao et al., 1999). It is important to point that some quality items were not applicable for the included studies in our systematic review (see Table 3). In addition, all of the included studies did not indicate the time period used for identifying participants, and did not describe how confounding variables were assessed and/or controlled. Thus, studies with good quality and an adequate representation should be implemented to investigate the effects of heat stress on immune system of older adults in natural environments. Larger samples from regions that have different hot temperatures with different humidity levels will give a better understanding of the consequences of heat stress on the health of older adults and their ability to adapt to the global warming. Furthermore, investigating the effects of heat stress on the immune system of older adult should also address health outcomes of the alterations of immune biomarkers. In the studies included in this review, the relationship between health or physiological parameters and dysregulation in immune biomarkers were not tested. Future studies of older adults with large population sample should investigate health problems that are related to heat-induce changes in immunity.

7. Conclusions

The role of the immune system in the ability of older adults to adapt and survive in response to heat stressors has surprisingly received little research attention so far, despite the imposing threats of global warming on their health and wellbeing. This systematic review yielded a modest number studies that met the inclusion criteria, which focused on investigating the direct effects of heat stress on immune biomarkers and possible adverse effects on health in among older adults. The findings from these studies showed consistent age-dependent dysregulation in immune biomarkers in response to heat exposure among older adults, which manifested in a wide range of dysregulations to interleukins and heat shock proteins (hsps), as well as alterations in biomarkers that regulates the immune system function such as cortisol and dopamine. This systematic review highlights the need for further studies on the role of the immune system in response and adaptation to heat stress, with a particular emphasis on older adults and within the context of global warming.

CRediT authorship contribution statement

Rabab Awad: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Assaf Suberry:** Visualization, Validation, Software, Investigation, Formal analysis, Data curation. **Ahmad Abu-Akel:** Writing – review & editing, Project administration, Methodology, Data curation, Conceptualization. **Liat Ayalon:** Writing – review & editing, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Author contribution

RA, AA and LA designed the study protocol. RA and AS participated in data collection, and “Title-abstract” and “Full text” screening. RA, AS and LA performed the quality assessment and interpretation of data. RA and LA conducted the handsearch. RA and AA drafted the manuscript writing, and LA and AS provided feedback and edits. Study was done under the supervision of LA.

Funding

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.exger.2025.112777.

Data availability

Data will be made available on request.

References

Adamo, S.A., Lovett, M.M., 2011. Some like it hot: the effects of climate change on reproduction, immune function and disease resistance in the cricket Gryllus texensis. J. Exp. Biol. 214 (12), 1997–2004. https://doi.org/10.1242/jeb.056531.

Al Meslamani, A.Z., 2024. How climate change influences pathogen transmission. Pathogens and Global Health 118 (5), 450–452. https://doi.org/10.1080/20477724.2023.2285185.

Al-Qahtani, A.A., Alhamlan, F.S., Al-Qahtani, A.A., 2024. Pro-inflammatory and anti-inflammatory interleukins in infectious diseases: a comprehensive review. Tropical medicine and infectious disease 9 (1), 13. https://doi.org/10.3390/tropicalmed9010013.

Amiri-Dashatan, N., Koushki, M., Parsamanesh, N., Chiti, H., 2022. Serum cortisol concentration and COVID-19 severity: a systematic review and meta-analysis. J. Investig. Med. 70 (3), 766–772. https://doi.org/10.1136/jim-2021-001989.

Balmain, B.N., Sabapathy, S., Louis, M., Morris, N.R., 2018. Aging and thermoregulatory control: the clinical implications of exercising under heat stress in older individuals. Biomed. Res. Int. 2018 (1), 8306154. https://doi.org/10.1155/2018/8306154.

Baranauskiene, N., Wang, J., Eimantas, N., Solianik, R., Brazaitis, M., 2023. Age-related differences in the neuromuscular performance of fatigue-provoking exercise under severe whole-body hyperthermia conditions. Scand. J. Med. Sci. Sports 33 (9), 1621–1637. https://doi.org/10.1111/sms.14403.

Bauer, M.E., 2005. Stress, glucocorticoids and ageing of the immune system. Stress 8 (1), 69–83. https://doi.org/10.1080/10253890500100240.

Beyeler, N., Salas, R.N., 2022. An unequivocal call to climate action for the health sector. bmj 376. https://doi.org/10.1136/bmj.o680.

Buford, T.W., Willoughby, D.S., 2008. Impact of DHEA (S) and cortisol on immune function in aging: a brief review. Appl. Physiol. Nutr. Metab. 33 (3), 429–433. https://doi.org/10.1139/H08-013.

Burek, K.A., Gulland, F.M., O'Hara, T.M., 2008. Effects of climate change on Arctic marine mammal health. Ecol. Appl. 18 (sp2), S126–S134. https://doi.org/10.1890/06-0553.1.

Caroprese, M., Bradford, B.J., Rhoads, R.P., 2021. Impact of climate change on immune responses in agricultural animals. Frontiers in Veterinary Science 8, 732203. https://doi.org/10.3389/fvets.2021.732203.

Chojnowska, S., Ptaszyńska-Sarosiek, I., Kępka, A., Knaś, M., Waszkiewicz, N., 2021. Salivary biomarkers of stress, anxiety and depression. J. Clin. Med. 10 (3), 517. https://doi.org/10.3390/jcm10030517.

Cianconi, P., Betrò, S., Janiri, L., 2020. The impact of climate change on mental health: a systematic descriptive review. Front. Psychol. 11, 490206. https://doi.org/10.3389/fpsyt.2020.00074.

Covidence, 2024. Covidence [Systematic review management software]. https://www.covidence.org.

Daëron, M., 2022. The immune system as a system of relations. Front. Immunol. 13, 984678. https://doi.org/10.3389/fimmu.2022.984678.

Day, M.J., 2010. Ageing, immunosenescence and inflammageing in the dog and cat. J. Comp. Pathol. 142, S60–S69. https://doi.org/10.1016/j.jcpa.2009.10.011.

Dhama, K., Latheef, S.K., Dadar, M., Samad, H.A., Munjal, A., Khandia, R., Karthik, K., Tiwari, M., Yatoo, I., Bhatt, B., Chakraborty, S., Singh, K.P., Iqbal, H., Chaicumpa, W., Joshi, S.K., 2019. Biomarkers in stress related diseases/disorders: diagnostic, prognostic, and therapeutic values. Front. Mol. Biosci. 6, 91. https://doi.org/10.3389/fmolb.2019.00091.

Eichberger, J., Resch, E., Resch, B., 2022. Diagnosis of neonatal sepsis: the role of inflammatory markers. Front. Pediatr. 10, 840288. https://doi.org/10.3389/fped.2022.840288.

Faresjö, T., Strömberg, S., Jones, M., Stomby, A., Karlsson, J.E., Östgren, C.J., Faresjö, A., Theodorsson, E., 2020. Elevated levels of cortisol in hair precede acute myocardial infarction. Sci. Rep. 10 (1), 22456. https://doi.org/10.1038/s41598-020-80559-9.

Field, C.B., Barros, V.R. (Eds.), 2014. Climate Change 2014–Impacts, Adaptation and Vulnerability: Regional Aspects. Cambridge University Press.

Foster, J., Mckenna, Z.J., Atkins, W.C., Jarrard, C.P., Crandall, C.G., 2023. Aging increases enterocyte damage during a 3-hour exposure to very hot and dry heat: a preliminary study. Biology 12 (8), 1088. https://doi.org/10.3390/biology12081088.

Franco, R., Reyes-Resina, I., Navarro, G., 2021. Dopamine in health and disease: much more than a neurotransmitter. Biomedicines 9 (2), 109. https://doi.org/10.3390/biomedicines9020109.

Habibi, P., Ostad, S.N., Heydari, A., Aliebrahimi, S., Montazeri, V., Foroushani, A.R., Monazzam, M.R., Ghazi- Khansari, M., Golbabaei, F., 2022. Effect of heat stress on DNA damage: a systematic literature review. Int. J. Biometeorol. 66 (11), 2147–2158. https://doi.org/10.1007/s00484-022-02351-w.

Harada, A., Sekido, N., Akahoshi, T., Wada, T., Mukaida, N., Matsushima, K., 1994. Essential involvement of interleukin-8 (IL-8) in acute inflammation. J. Leukoc. Biol. 56 (5), 559–564. https://doi.org/10.1002/jlb.56.5.559.

Hawkley, L.C., Cacioppo, J.T., 2004. Stress and the aging immune system. Brain Behav. Immun. 18 (2), 114–119. https://doi.org/10.1016/j.bbi.2003.09.005.

Hu, C., Yang, J., Qi, Z., Wu, H., Wang, B., Zou, F., Mei, H., Liu, J., Wang, W., Liu, Q., 2022. Heat shock proteins: biological functions, pathological roles, and therapeutic opportunities. MedComm 3 (3), e161. https://doi.org/10.1002/mco2.161.

Islam, A., Hait, S.H., Andrews-Shigaki, B., Carus, S., Deuster, P.A., 2014. Plasma HSP70 levels correlate with health risk factors and insulin resistance in African American subjects. Exp. Clin. Endocrinol. Diabetes 122 (08), 496–501. https://doi.org/10.1055/s-0034-1374636.

Jafari, M.J., Pirposhteh, E.A., Dehghan, S.F., Khodakarim, S., Jafari, M., 2020a. Relationship between heat stress exposure and some immunological parameters among foundry workers. Int. J. Biometeorol. 64 (5), 853–861. https://doi.org/10.1007/s00484-020-01874-4.

Jafari, M.J., Pirposhteh, E.A., Dehghan, S.F., Khodakarim, S., Jafari, M., 2020b. Relationship between heat stress exposure and some immunological parameters among foundry workers. Int. J. Biometeorol. 64 (5), 853–861. https://doi.org/10.1007/s00484-020-01874-4.

Jurivich, D.A., Choo, M., Welk, J., Qiu, L., Han, K., Zhou, X., 2005. Human aging alters the first phase of the molecular response to stress in T-cells. Exp. Gerontol. 40 (12), 948–958. https://doi.org/10.1016/j.exger.2005.08.003.

Kamin, H.S., Kertes, D.A., 2017. Cortisol and DHEA in development and psychopathology. Horm. Behav. 89, 69–85. https://doi.org/10.1016/j.yhbeh.2016.11.018.

Khan, U., Ghazanfar, H., 2018. T lymphocytes and autoimmunity. Int. Rev. Cell Mol. Biol. 341, 125–168. https://doi.org/10.1016/bs.ircmb.2018.05.008.

Kotcher, J., Maibach, E., Miller, J., Campbell, E., Alqodmani, L., Maiero, M., Wyns, A., 2021. Views of health professionals on climate change and health: a multinational survey study. The Lancet Planetary Health 5 (5), e316–e323. https://doi.org/10.1016/S2542-5196(21)00053-X.

Labad, J., 2019. The role of cortisol and prolactin in the pathogenesis and clinical expression of psychotic disorders. Psychoneuroendocrinology 102, 24–36. https://doi.org/10.1016/j.psyneuen. 2018.11.028.

Lau, E., Marques, C., Pestana, D., Santoalha, M., Carvalho, D., Freitas, P., Calhau, C., 2016. The role of I-FABP as a biomarker of intestinal barrier dysfunction driven by gut microbiota changes in obesity. Nutrition & metabolism 13, 1–7. https://doi.org/10.1186/s12986-016-0089-7. PMID: 27134637; PMCID: PMC4851788.

Leyk, D., Hoitz, J., Becker, C., Glitz, K.J., Nestler, K., Piekarski, C., 2019. Health risks and interventions in exertional heat stress. Dtsch. Arztebl. Int. 116 (31−32), 537. https://doi.org/10.3238/arztebl.2019.0537. PMID: 31554541; PMCID: PMC6783627.

Liu, A.Y., Minetti, C.A., Remeta, D.P., Breslauer, K.J., Chen, K.Y., 2022. HSF1, aging, and neurodegeneration. Cell biology and translational medicine, volume 18: tissue differentiation, repair in health and disease 23–49. https://doi.org/10.1007/5584_2022_733.

Mälzer, J.N., Schulz, A.R., Thiel, A., 2016. Environmental influences on the immune system: the aging immune system. Environmental Influences on the Immune System 55-76. https://doi.org/10.1007/978-3-7091-1890-0_3.

Mapunda, J.A., Tibar, H., Regragui, W., Engelhardt, B., 2022. How does the immune system enter the brain? Front. Immunol. 13, 805657. https://doi.org/10.3389/fimmu.2022.805657.

Millyard, A., Layden, J.D., Pyne, D.B., Edwards, A.M., Bloxham, S.R., 2020. Impairments to thermoregulation in the elderly during heat exposure events. Gerontology and Geriatric Medicine 6, 2333721420932432. https://doi.org/10.1177/2333721420932432. 32596421. PMC7297481.

Parkin, J., Cohen, B., 2001. An overview of the immune system. Lancet 357 (9270), 1777–1789. https://doi.org/10.1016/S0140-6736(00)04904-7.

Patz, J.A., Olson, S.H., 2006. Climate change and health: global to local influences on disease risk. Ann. Trop. Med. Parasitol. 100 (5–6), 535–549. https://doi.org/10.1179/136485906X97426.

Perry, D., 2017. Climate change and the evolution of insect immune function. Available from: http://purl.fcla.edu/fcla/etd/CFE0006638.

Phillips, A.C., Burns, V.E., Lord, J.M., 2007. Stress and exercise: getting the balance right for aging immunity. Exerc. Sport Sci. Rev. 35 (1), 35–39. https://doi.org/10.1097/jes.0b013e31802d7008 (PMID: 17211192).

Pirchio, R., Graziadio, C., Colao, A., Pivonello, R., Auriemma, R.S., 2022. Metabolic effects of prolactin. Front. Endocrinol. 13, 1015520. https://doi.org/10.3389/fendo.2022.1015520.

Qu, B., Jia, Y., Liu, Y., Wang, H., Ren, G., Wang, H., 2015. The detection and role of heat shock protein 70 in various nondisease conditions and disease conditions: a literature review. Cell Stress Chaperones 20 (6), 885–892. https://doi.org/10.1007/s12192-015-0618-8.

Rao, D.V., Watson, K., Jones, G.L., 1999. Age-related attenuation in the expression of the major heat shock proteins in human peripheral lymphocytes. Mech. Ageing Dev. 107 (1), 105–118. https://doi.org/10.1016/S0047-6374(98)00143-2.

Rostom, A., Dubé, C., Cranney, A., Saloojee, N., Sy, R., Garritty, C., Patel, D., 2004. Appendix C. Data Assessment and Data Abstraction Forms. In Celiac Disease, Agency for Healthcare Research and Quality (US).

Saia, R.S., Giusti, H., Luis-Silva, F., Pedroso, K.D.J.B., Auxiliadora-Martins, M., Morejón, K.M.L., Nogueira, R.J.N., Scarante, F.F., Franco, M.I., Sato, M.T., Assis, F. V., Carmona, M.J.C., Basile-Filho, A., 2021. Clinical investigation of intestinal fatty acid-binding protein (I-FABP) as a biomarker of SARS-CoV-2 infection. Int. J. Infect. Dis. 113, 82–86. https://doi.org/10.1016/j.ijid.2021.09.051.

Starkie, R.L., Hargreaves, M., Rolland, J., Febbraio, M.A., 2005a. Heat stress, cytokines, and the immune response to exercise. Brain Behav. Immun. 19 (5), 404–412. https://doi.org/10.1016/j.bbi.2005.03.005.

Starkie, R.L., Hargreaves, M., Rolland, J., Febbraio, M.A., 2005b. Heat stress, cytokines, and the immune response to exercise. Brain Behav. Immun. 19 (5), 404–412. https://doi.org/10.1016/j.bbi.2005.03.005.

Studerus, E., Ittig, S., Beck, K., Del Cacho, N., Vila-Badia, R., Butjosa, A., Rodriguez, V., Nunez, M., Moreno, C., Romero, S., Bonnin, C.D.M., Bioque, M., Parellada, M., Lobo, A., Bernardo, M., Riecher-Rössler, A., 2021. Relation between self-perceived stress, psychopathological symptoms and the stress hormone prolactin in emerging psychosis. J. Psychiatr. Res. 136, 428–434. https://doi.org/10.1016/j.jpsychires.2020.06.014.

Sudheimer, K.D., O'Hara, R., Spiegel, D., Powers, B., Kraemer, H.C., Neri, E., Weiner, M., Hardan, A., Hallmayer, J., Dhabhar, F.S., 2014. Cortisol, cytokines, and hippocampal volume interactions in the elderly. Front. Aging Neurosci. 6, 153. https://doi.org/10.3389/fnagi.2014.00153.

Tansey, M.G., Wallings, R.L., Houser, M.C., Herrick, M.K., Keating, C.E., Joers, V., 2022. Inflammation and immune dysfunction in Parkinson disease. Nat. Rev. Immunol. 22 (11), 657–673. https://doi.org/10.1038/s41577-022-00684-6.

Tsai, S.J., 2021. Role of interleukin 8 in depression and other psychiatric disorders. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 106, 110173. https://doi.org/10.1016/j.pnpbp.2020.110173.

Tsan, M.F., Gao, B., 2009. Heat shock proteins and immune system. Journal of Leucocyte Biology 85 (6), 905–910. https://doi.org/10.1189/jlb.0109005.

Tylutka, A., Walas, Ł., Zembron-Lacny, A., 2024. Level of IL-6, TNF, and IL-1β and age-related diseases: A systematic review and meta-analysis. Frontiers in Immunology 15, 1330386. https://doi.org/10.3389/fimmu.2024.1330386.

Weng, Y.C., Chen, W.T., Lee, J.C., Huang, Y.N., Yang, C.K., Hsieh, H.S., Hsu, C.W., Chang, W.C., Lin, Y.C., Tsai, H.C., Lu, Y.B., 2021. Intestinal fatty acid-binding protein is a biomarker for diagnosis of biliary tract infection. JGH Open 5 (10), 1160–1165. https://doi.org/10.1080/00365521.2023.2229930.

Witkowski, M., Landmesser, U., Rauch, U., 2016. Tissue factor as a link between inflammation and coagulation. Trends Cardiovasc. Med. 26 (4), 297–303. https://doi.org/10.1016/j.tcm.2015.12.001.

Wu, X., Lu, Y., Zhou, S., Chen, L., Xu, B., 2016. Impact of climate change on human infectious diseases: empirical evidence and human adaptation. Environ. Int. 86, 14–23. https://doi.org/10.1016/j.envint.2015.09.007.

Zannas, A.S., 2024. Biological aging and mental illness—a vicious cycle? JAMA Psychiatry 81 (5), 433–434. https://doi.org/10.1001/jamapsychiatry.2024.0084.

Zheng, B., Tal, R., Yang, Z., Middleton, L., Udeh-Momoh, C., 2020. Cortisol hypersecretion and the risk of Alzheimer's disease: a systematic review and meta-analysis. Ageing Res. Rev. 64, 101171. https://doi.org/10.1016/j.arr.2020.101171.

Zhou, J., Zhu, L., Li, Y., 2023. Association between the triglyceride glucose index and diabetic retinopathy in type 2 diabetes: a meta-analysis. Front. Endocrinol. 14, 1302127. https://doi.org/10.3389/fendo.2023.1302127.