Effects of extreme heat on physiology, morbidity, and mortality under climate change: mechanisms and clinical implications

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ABSTRACT

Climate change is escalating the frequency and severity of extreme heat events, significantly augmenting disease burden through heat exposure. However, understanding of the underlying mechanisms remains insufficient, hindering the development of targeted interventions for heat related illnesses. This review summarizes the multifaceted mechanisms by which heat exposure induces systemic and organ specific damage. It elucidates how heat stress not only triggers systemic physiological dysfunction but also exacerbates specific organ injuries, thereby increasing morbidity and mortality risks across populations. These mechanisms drive shifts in disease profiles toward acute heat related illnesses, cardiovascular diseases, renal disorders, and other conditions, particularly affecting vulnerable groups. Susceptibility to heat exposure spans the entire life course, from prenatal stages to old age, and is amplified by socioeconomic disparities. The review proposes initiatives to reduce negative health outcomes and advocates for the integration of heat exposure into clinical practice guidelines, to safeguard public health in an era of unprecedented thermal challenges.

Introduction

Extreme heat events have increased in frequency, duration, and severity because of climate change.[1] Under current mitigation agreements, global temperatures are projected to rise by 2.7°C above pre-industrial levels by 2100.[2] Heat exposure poses serious threats to human health, driving elevated risks of morbidity and mortality by inducing multisystem physiological dysfunction.[3 4] Notably, health risks associated with heat exposure persist throughout the lifespan.[5-7] Understanding the multifaceted effects of heat exposure under climate change is crucial for minimizing its detrimental effects on population health.

Despite comprehensive epidemiological studies showing robust associations between heat exposure and adverse health outcomes, particularly for cardiovascular, respiratory, and renal diseases, mechanistic insights into the pathophysiological pathways driving these effects remain fragmented.[8-10] Although several reviews have examined the health effects of heat exposure, many lack detailed mechanistic insights or focus narrowly on single organ systems, with few integrating evidence from a multisystem damage perspective.[1 11 12] The limited mechanistic understanding may impede the development of targeted interventions, leaving public health strategies reliant on clinical endpoint management rather than primary prevention. Therefore, a paradigm shift toward elucidating the multisystem damage of heat exposure is essential to close this critical gap.

This review seeks to bridge this knowledge gap by comprehensively summarizing current understanding of how heat exposure affects multiple systems, highlighting the key biological mechanisms involved. On the basis of the integrated mechanism framework of multisystem dysfunction, we further discuss the future transitions in disease spectrum and susceptibility of vulnerable populations, and we provide policy makers and healthcare professionals with targeted strategies to reduce the escalating burden of heat sensitive diseases in the context of climate change.

Sources and selection criteria

We did literature searches for this narrative review in PubMed and Embase from February to August 2025. We used the following search terms and their database specific modifications (that is, MeSH terms in PubMed) to identify relevant articles: “heatwave”, “high temperature”, “climate change”, “global warming”, “extreme heat”, “heatstroke”, “cardiovascular disease”, “respiratory disease”, “kidney disease”, “endocrine”, “neurological disease”, “digestion”, “immune”, and “reproduction”, as well as other

disease and biological mechanism specific keywords discussed in this review. We prioritized peer reviewed articles in English, with emphasis on publication in high impact journals, thematic relevance, research quality, and geographic representativeness. We included observational studies, case series, randomized controlled trials, systematic reviews, guidelines, meta-analyses focusing on the effects of high temperatures on multisystem diseases, and robust evidence from animal studies and laboratory experiments in the mechanistic insights section. We considered studies published between 1 January 2000 and 31 August 2025, with preference given to those from the past decade. We excluded articles that were not peer reviewed or not available in English.

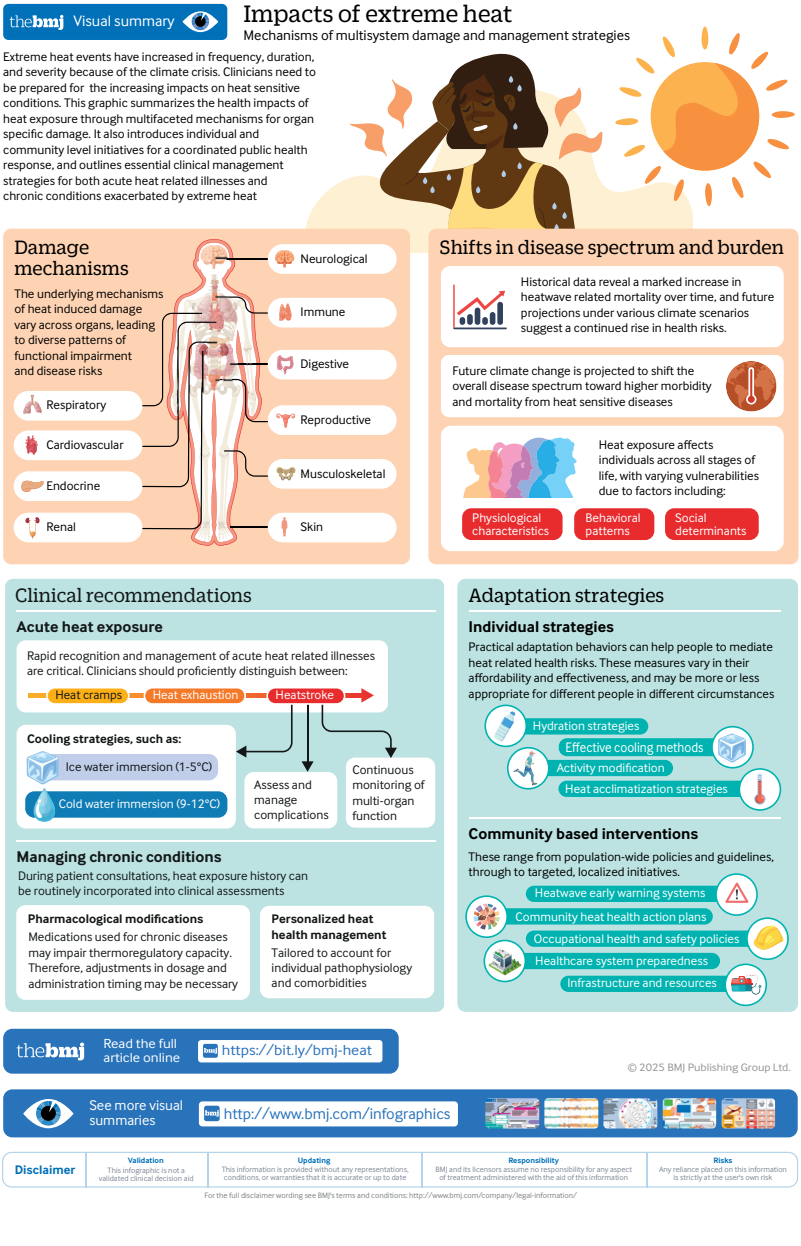
Epidemiology

Heat exposure is a driver of excess mortality, with global and regional studies consistently linking high temperatures to elevated risks of all cause and cause specific deaths.[13] Globally, heat related mortality among people aged over 65 has risen by 167% in 2023 compared with the 1990s.[14] Evidence from 43 countries shows that 37.0% (95% confidence interval (CI) 20.5% to 76.3%) of warm season heat related deaths from 1991 to 2018 can be attributed to anthropogenic climate change.[15] In 272 Chinese cities, moderate and extreme heat account for 2.08% and 0.63% of total mortality, respectively.[16] Cardiovascular disease emerges as the major heatwave related cause of death,[17] supported by a global meta-analysis showing a 12% increase in cardiovascular disease related mortality risk during heatwaves (relative risk 1.12, 95% CI 1.09 to 1.14). Each 1°C temperature rise increases cardiovascular disease mortality by 2.1% and morbidity by 0.5%, with increased risks for stroke, coronary heart disease, and heart failure as well.[18]

Beyond mortality, epidemiological evidence links heat exposure to diverse multisystem health effects (fig 1). In China, heatwaves are reported to be associated with an 11.6% (95% CI 6.9% to 16.6%) increase in risk of admission to hospital for chronic kidney disease compared with non-heatwave periods.[19] Evidence from a US meta-regression analysis links higher temperatures to increased incidence of diabetes.[20] An Australian study reports elevated emergency visits and ambulance callouts for respiratory conditions during heatwaves.[21] Heat exposure is also associated with neurological and mental health outcomes, including cognitive impairment, dementia, Parkinson's disease, depression, and anxiety.[22 23] In Australia, high temperatures have been reported to contribute to an annual loss of 8458 disability adjusted life years, representing 1.8% of the total burden of mental and behavioral disorders.[24] A multi-country meta-analysis shows a 16% increased risk of preterm birth during heatwaves, with a 1.05-fold (95% CI 1.03 to 1.07) rise per 1°C temperature increase, as well as a similar increase in stillbirths.[25] Notably, identified physiological mechanisms provide biological plausibility and mechanistic support for the observed epidemiological evidence, positioning the epidemiological findings as real world outcomes of fundamental pathophysiological processes.

Shifting disease spectrum under climate change

Historical data show a marked increase in heatwave related mortality over time, and future projections under various climate scenarios suggest a continued rise in health risks.[26] Global evidence from the Multi-Country Multi-City Collaborative Research Network indicates that the increased risk of heat related mortality has already been evident over the past two decades and remains a continuing future threat.[27] Projections in China indicate a substantial rise in heatwave attributable mortality by 2090, with estimated annual deaths of 20 303 under representative concentration pathway (RCP)2.6, 35 025 under RCP4.5, and 72 260 under RCP8.5.[28]



Under the shared socioeconomic pathway 5-8.5 scenario, accounting for demographic and mortality trends, heat related mortality among children in Africa is projected to double by 2049 compared with 2005-14.[29] Furthermore, emerging evidence highlights significant increases in other heat related health risks attributable to anthropogenic climate change, such as cardiovascular disease and diabetes.[30 31] For instance, compared with the 2010s, the attributable fraction for heat related stroke mortality is projected to rise by 0.8% to 7.5% across 22 East Asian cities by the 2090s under different climate scenarios.[31]

Future climate change is projected to intensify heat exposure, thereby shifting the overall disease spectrum and reshaping the global disease landscape. Increasingly frequent and severe heatwaves are expected to increase risks of acute heat related illnesses, including heat rash, heat cramps, heat edema, heat syncope, heat exhaustion, and heatstroke.[32] A clear shift is expected toward higher morbidity and mortality from other heat sensitive diseases, particularly those affecting the cardiovascular, respiratory, and renal systems.[33 34]

Concurrently, previously less recognized heat associated health risks, such as adverse birth outcomes, gestational diabetes, neurodegenerative disease, and mental disorders, are emerging as significant contributors to the disease burden.[35 36] Rising temperatures are also linked to increased risks of transmission of infectious diseases, especially vectorborne and waterborne illnesses, owing to temperature sensitive pathogenic and vector dynamics.[37] Climate induced shifts in temperature may further alter the seasonal and geographic distribution of temperature sensitive diseases. For example, cold related conditions such as hypothermia, frostbite, and certain respiratory infections are projected to decline in many regions as a result of milder and shorter winters.[38]

Mechanisms of multisystem damage from heat exposure

When exposed to heat, human physiology initiates adaptive responses via two primary mechanisms: cutaneous vasodilation to enhance core to surface heat dissipation and increased sweating to promote evaporative cooling.[1] Specifically, the hypothalamus regulates body temperature by integrating peripheral temperature receptors distributed in the skin, core organs, and spinal cord, enabling real time thermoregulatory adjustments.[39] The endocrine system contributes to heat adaptation through the release of hormones such as antidiuretic hormone, aldosterone, and cortisol, and activation of the autonomic nervous system exerts systemic effects.[12 40] During mild to moderate heat exposure, these adaptation mechanisms may enable effective thermoregulation and maintain thermal homeostasis. However, extreme heat exposure can overwhelm these compensatory thermoregulatory mechanisms, leading to systemic damage.

Heat induced fluid loss leads to electrolyte imbalances, including hypokalemia or hyperkalemia and hypomagnesemia.[41] Thermal stress triggers systemic inflammation, characterized by elevated

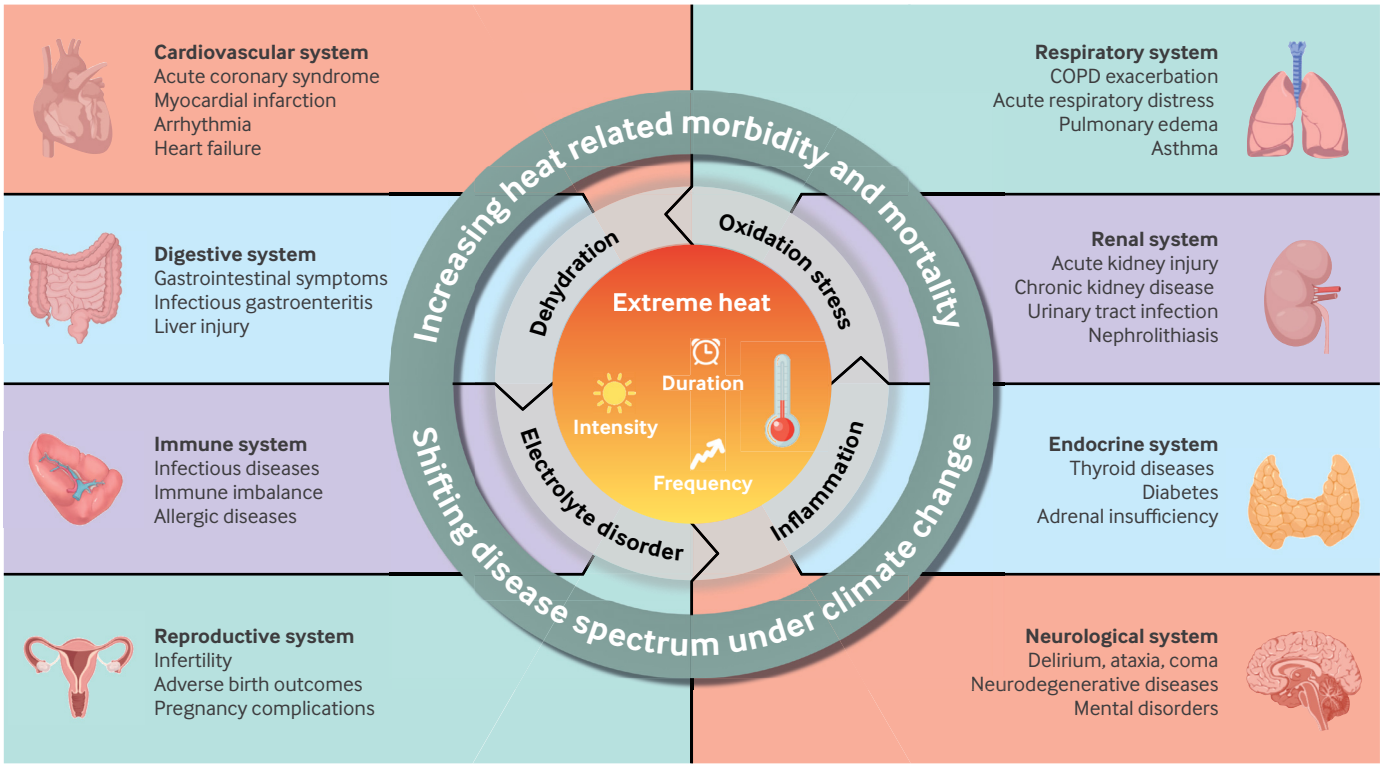


Fig 1 | Risk of multisystem diseases associated with exposure to extreme heat. COPD=chronic obstructive pulmonary disease

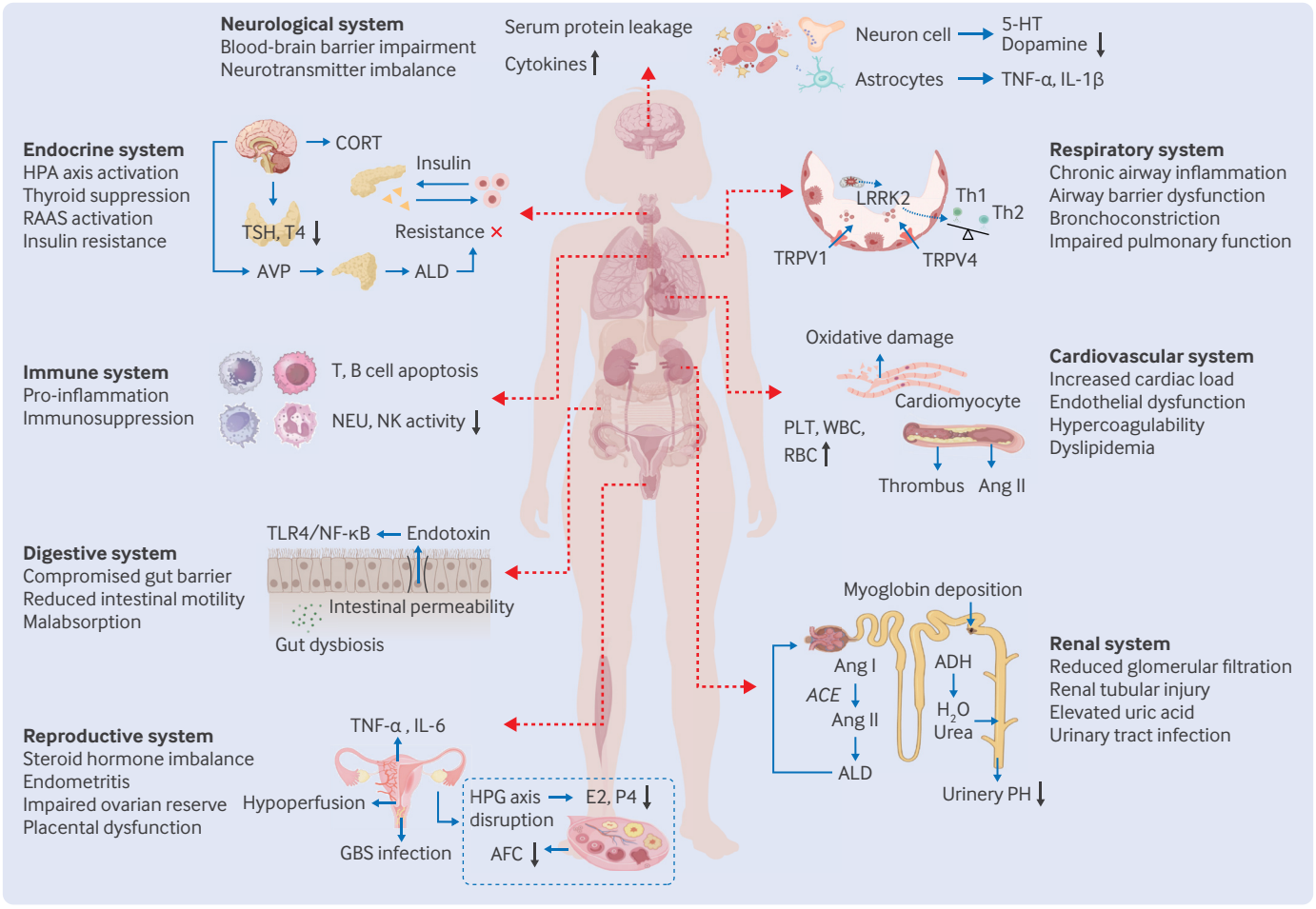


Fig 2 | Mechanisms of multisystem damage induced by extreme heat exposure. 5-HT=5-hydroxytryptamine; ACE=angiotensin converting enzyme; ADH=antidiuretic hormone; AFC=antral follicle count; ALD=aldosterone; Ang I=angiotensin I; Ang II=angiotensin II; AVP=arginine vasopressin; B cell=B lymphocyte; CORT=cortisol; E2=estradiol; GBS=group B *Streptococcus*; HPA=hypothalamic-pituitary-adrenal axis; HPG=hypothalamic-pituitary-gonadal axis;IL-1β=interleukin 1 β; IL-6=interleukin 6; LRRK2=leucine-rich repeat kinase 2; NEU=neutrophil; NF-κB=nuclear factor κ light chain enhancer of activated B cells; NK=natural killer cell; P4=progesterone; PLT=platelet; RAAS=renin-angiotensin-aldosterone system; RBC=red blood cell; T4=thyroxine; T cell=T lymphocyte; Th1=T helper 1 cell; Th2=T helper 2 cell; TLR4=toll-like receptor 4; TNF-α=tumor necrosis factor-α; TRPV1=transient receptor potential vanilloid 1; TRPV4=transient receptor potential vanilloid 4; TSH=thyroid stimulating hormone; WBC=white blood cell

concentrations of pro-inflammatory cytokines, such as interleukin 1β, interleukin 6, interferon-γ, tumor necrosis factor-α (TNF-α), and high sensitivity C reactive protein.[11 42] Concurrently, oxidative stress activates protective pathways, notably the upregulation of heat shock proteins, which preserve protein integrity, inhibit apoptosis, and enhance thermotolerance.[43 44] The underlying mechanisms of heat induced damage vary across organs, leading to diverse patterns of functional impairment and disease risks (fig 2).

Cardiovascular system

Heat exposure elevates heart rate and blood flow, leading to higher cardiovascular workload. Cutaneous vasodilation increases cardiac output, requiring the heart to pump harder and faster, thereby increasing oxygen demand in coronary tissues. A multilevel mixed effects meta-analysis shows that for each 1°C rise in core temperature, heart rate increases by 26 (95% CI 22 to 29) bpm, cardiac output by 1.0 (0.4 to 1.6) L/min, and rate pressure product, a biomarker of cardiac workload, by 1841 (32 to 3650) mm Hg×bpm/min.[45] Elevated core temperature and resultant volume depletion trigger sympathetic nervous system activation to maintain blood pressure by increasing heart rate and stroke volume.[46] In people with pre-existing cardiovascular disease, this response may precipitate demand ischemia or plaque rupture.[47] Concurrently, heat induced electrolyte imbalances can disrupt myocardial ion channel function, impairing electrical stability and increasing the risk of arrhythmia.[48]

Extreme heat causes myocardial injury through multiple mechanisms, including cardiomyocyte apoptosis, oxidative damage, and myocardial ischemia, thereby impairing endothelial function.[49 50] Evidence from animal models indicates

that heat stress elevates oxidative damage and triggers cardiomyocyte apoptosis via activation of the angiotensin II signaling pathway.[51] Hyperthermia induced dehydration leads to hemoconcentration and a hypercoagulable state, synergistically increasing the risks of thrombosis and myocardial infarction.[46 48] For example, heat exposure has been linked to increased platelet counts, leukocytosis, and erythrocytosis.[48] Coagulation profiles, observed in epidemiological studies, show shortened activated partial thromboplastin time and prothrombin time, prolonged thrombin time, and elevated fibrinogen concentrations associated with heat exposure, indicating enhanced activation of both intrinsic and extrinsic coagulation pathways.[52] In addition, chronic heat exposure also disrupts lipid metabolism by increasing low density lipoprotein and decreasing high density lipoprotein concentrations, thereby promoting dyslipidemia.[53] Taken together, these pathophysiological disturbances are hypothesized to represent key mechanisms by which heat exposure increases the risk of cardiovascular events, including myocardial infarction,[54] stroke,[55] and heart failure.[11]

Respiratory system

Acute lung inflammation and lung injury have been observed in patients with heatstroke.[56] Heat derived lung damage, manifesting as pulmonary edema and acute respiratory distress syndrome, coupled with pulmonary stress due to heat related hyperventilation, significantly contributes to respiratory dysfunction.[57] Experimental evidence indicates that leucine-rich repeat kinase 2 may be involved in heat induced acute lung injury and alveolar type II epithelial cell dysfunction.[58]

Mouse models suggest that high temperatures exacerbate airway inflammation by elevating concentrations of interleukin 4, interleukin 1β, interleukin 6, and TNF-α, thereby altering mucus production and damaging the airway epithelium.[59] Early molecular events described above initiate a cascade of effects that promote airway hyperreactivity. Extreme heat activates bronchopulmonary vagal C fibers via stimulation of transient receptor potential vanilloid (TRPV) 1 and TRPV4.[60] This activation induces reflex bronchoconstriction, increased airway resistance, and compensatory hyperventilation marked by elevated tidal volume and respiratory rate.[61 62] Collectively, these pathways may represent core mechanisms through which heat exposure exacerbates pre-existing respiratory conditions such as chronic obstructive pulmonary disease (COPD) and asthma.[63 64]

Heat exposure has been associated with decreased pulmonary function, particularly among people with chronic respiratory diseases. For instance, a longitudinal study among adults with asthma across 25 Chinese cities indicates that extreme high temperature is associated with decreases of 26.0 mL in forced expiratory volume in 1 second, 35.8 mL/s in peak expiratory flow, and 23.4 mL in forced vital capacity.[65] A randomized crossover trial in 30 healthy adults also links acute heat exposure to impaired lung function, potentially via mechanisms including lung epithelial damage, airway inflammation, and disrupted airway microbiota.[66] Beyond exacerbating chronic respiratory diseases, heat exposure also heightens the risk of respiratory infections through dysregulation of pulmonary immunity. Chronic heat exposure increases susceptibility to respiratory pathogens through depletion of alveolar macrophages and consequent local immune dysfunction.[67] Moreover, extreme heat promotes allergic asthma by shifting the T helper 1 (Th1)/Th2 balance toward Th2 dominance, leading to increased eosinophilic inflammation mediated by Th2.[61]

Renal system

Extreme heat exposure leads to dehydration, not only reducing circulatory renal blood volume but also impairing glomerular filtration rate, potentially progressing to acute kidney injury (AKI) or even renal failure.[68] AKI, often resulting from renal hypoperfusion and hypoxia, is a common complication of heatstroke. It manifests as two subtypes: exertional heatstroke, typically associated with rhabdomyolysis; and epidemic heatstroke, with normal or mildly elevated creatine phosphokinase concentrations.[69] Rhabdomyolysis associated AKI is primarily mediated by myoglobin toxicity,[70] whereas the second subtype is characterized by acute interstitial nephritis, presenting with urinary leukocytosis, hematuria, and tubulointerstitial damage.[69] Reduced renal blood flow impairs delivery of nutrients to tubular cells and triggers inflammation and necrosis.[71] Injured tubular cells release damage associated molecular patterns that activate immune and non-immune cells via pattern recognition receptors such as toll-like receptors, promoting the release of pro-inflammatory mediators.[69]

Evidence suggests that recurrent AKI, triggered by heatstroke, may contribute to development of chronic kidney disease (CKD).[72 73] Animal studies have shown that repeated heat stress leads to chronic inflammation and progressive tubular injury.[74] Clinical findings further indicate that heat and dehydration promote the production of concentrated and acidic urine, which predisposes to urate crystallization.[75] The underlying mechanism is mediated by the polyol-fructokinase pathway and arginine vasopressin.[74] Recurrent hyperosmolality activates the polyol pathway, triggering local fructose production, which is subsequently metabolized in the proximal tubule to release uric acid.[76] Concomitant dehydration stimulates arginine vasopressin release from the neurohypophysis, promoting water and urea reabsorption in the renal tubules, reducing urinary volume and concentrating urine.[77] Elevated urate concentrations also increase synthesis of reactive oxygen species (ROS) and promote endothelial damage, further exacerbating progression of CKD.[78] Importantly, people with pre-existing CKD, particularly those undergoing dialysis,

are at increased risk during heat exposure owing to impaired thermoregulation.[79]

Reduced renal blood flow associated with heat exposure activates the renin-angiotensin-aldosterone system (RAAS), which not only exacerbates renal vasoconstriction but also triggers cardiovascular events among patients with CKD.[68 80] Urine concentration and acidification increase calcium supersaturation, promoting crystallization and stone formation, thereby raising the risk of nephrolithiasis.[81] Reduced urine output caused by dehydration further impairs bacterial clearance and enhances susceptibility to urinary tract infections (UTI). Evidence from California shows a 7.3% (95% CI 5.6% to 9.1%) increase in UTI related hospital admissions per 10°F elevation in warm season temperature.[82]

Endocrine system

Hormonal imbalances lead to compromised heat dissipation through sweat gland dysfunction and reduced cutaneous perfusion. Meanwhile, extreme heat exposure activates or suppresses stress hormone pathways, which may exacerbate multiaxial endocrine disorders, highlighting a bidirectional relation between thermal stress and endocrine dysregulation.[12]

Heat stress stimulates the hypothalamic-pituitary-adrenal (HPA) axis, increasing the release of cortisol, which closely correlates with acute rises in core temperature.[83] Thyroid hormones, which regulate metabolic rate, are also influenced by ambient temperature.[12] Epidemiological and animal studies both indicate that heat stress may suppress plasma concentrations of thyroid stimulating hormone, tetraiodothyronine, and triiodothyronine.[84 85] Moreover, heat exposure can impair the peripheral conversion of tetraiodothyronine to triiodothyronine, with the resultant low triiodothyronine concentrations aiding thermoregulation by lowering metabolic heat production.[12] People with thyroid disorders, such as hyperthyroidism, are theoretically at increased risk of heat related illness, although quantitative risk estimates remain limited.[12]

Heat stress activates the RAAS, increasing aldosterone, and stimulates temperature sensitive arginine vasopressin release.[68] Elevated concentrations of aldosterone and arginine vasopressin contribute to the regulation of water balance by reducing sodium and water excretion, respectively.[86 87] Epidemiological evidence also shows a dose dependent association between ambient heat exposure and disrupted glucose homeostasis.[88] Heat induced insulin resistance mainly arises through two pathways: dehydration directly impairs insulin signaling,[89] and reduced brown adipose tissue activity increases fatty acid flux to metabolically active tissues such as skeletal muscle, thereby decreasing insulin mediated glucose uptake.[20]

Neurological system

Heatstroke can cause cerebral injury through metabolic encephalopathy, vasogenic edema, ischemic hypoxia, and hypernatremic encephalopathy, leading to acute neuropsychiatric disturbances such as delirium, ataxia, and coma.[22] Heat stress also elicits neuroinflammation, thereby exacerbating cerebral injury.[90] For example, microglia and astrocytes can be activated by heat exposure, which leads to the release of pro-inflammatory cytokines and exacerbates neurodegenerative pathologies.[91 92] Hyperthermia further damages cerebrovascular endothelial cells, compromising the integrity of the blood-brain barrier. Subsequent leakage of serum proteins and inflammatory mediators exacerbates cerebral edema, culminating in elevated intracranial pressure.[93]

Peripheral vasodilation induced by thermal stress diverts cerebral perfusion, impairing neurovascular coupling and precipitating hypoperfusion related cognitive deficits. Simultaneously, heat stress amplifies neuronal energy demands during cognitive processing and accelerates depletion of metabolic reserves.[94 95] In addition, hyperthermia suppresses synthesis and release of 5-hydroxytryptamine, attenuating its neuromodulatory effects on emotional and cognitive processing. Heat induced dopaminergic dysfunction may further exacerbate neuropsychiatric comorbidities.[96 97] A randomized crossover study in 20 college students identifies brain derived neurotrophic factor, γ-aminobutyric acid, and adrenal glucocorticoids as biomarkers of heat stress induced anxiety.[98] Extreme heat also disturbs sleep architecture, manifesting as fragmented sleep and reduced rapid eye movement and non-rapid eye movement stage 3 (N3) sleep phases, subsequently impairing cognition and emotional regulation.[99]

Digestive system

Hyperthermia directly damages intestinal mucosal integrity through structural disruption of epithelial tight junction proteins.[100] The resulting increase in gut permeability enables the translocation of endotoxins and inflammatory mediators into the systemic circulation, amplifying systemic inflammation.[101 102] The increased pro-inflammatory cascades can damage other organs, including the pancreas and liver.[103] An in vitro study on heat induced intestinal injury suggests that crosstalk between endoplasmic reticulum stress and oxidative stress contributes to apoptosis.[104]

Redistribution of blood flow diverts perfusion from the gut to the skin, leading to intestinal hypoperfusion.[105] Additionally, heat stress disrupts the HPA axis and parasympathetic signaling, suppressing intestinal peristalsis and prolonging retention of digestive enzymes.[106 107] A randomized crossover study in 10 young healthy men indicates that heat exposure results in a significant decrease in plasma ghrelin.[108] These pathways are hypothesized to predispose individuals to malabsorption syndromes and even contribute to acute gastrointestinal symptoms such as nausea and vomiting.[109 110]

Additionally, hyperthermia disrupts the gut microbiome and increases susceptibility to gastrointestinal infections and inflammation.[111 112] Notably, extreme heat exacerbates water contamination by accelerating the proliferation of pathogens, including viruses and bacteria such as *Salmonella*, *Vibrio cholerae*, and *Shigella* spp, thereby increasing the incidence of infectious diarrheal diseases.[4 113]

Immune system

As mentioned above, extreme heat can disrupt the homeostasis between pro-inflammatory and anti-inflammatory regulation. Emerging evidence links sustained environmental heat exposure to immune cell activation and the systemic release of pro-inflammatory cytokines.[114] Additionally, heat induced increases in gut permeability facilitate the translocation of endotoxins into the systemic circulation, activating the toll-like receptor 4 (TLR4)/nuclear factor κ light chain enhancer of activated B cells (NF-κB) signaling pathway and further amplifying pro-inflammation.[115 116] Although the body activates compensatory anti-inflammation through the release of interleukin 1Ra, interleukin 10, and soluble TNF receptors,[117] they are insufficient to counterbalance the dominant pro-inflammatory response induced by thermal stress.[118]

Heat exposure also disrupts immune function through the endocrine-immune axis. Activation of the HPA axis increases cortisol, which induces apoptosis of T and B lymphocytes, reduces neutrophil and natural killer cell activity, and promotes polarization of M2 macrophages.[119 120] Consequently, prolonged heat stress leads to immunosuppression, characterized by impaired pathogen clearance and reduced immune cell recruitment to infection sites, thereby increasing susceptibility to pathogens.[118 119] Notably, transient receptor potential channels activated by higher temperatures contribute to the release of pro-inflammatory cytokines such as interleukin 25, interleukin 33, and Th2-type interleukins, thereby exacerbating allergic diseases, particularly asthma.[121]

Reproductive system

Heat exposure can decrease plasma testosterone and diminish fertility.[12] Human spermatogenesis is temperature sensitive, with scrotal hyperthermia decreasing sperm output and quality.[122] Extreme heat impairs spermatogenesis primarily through mitochondria dependent and death receptor mediated apoptotic pathways, as well as endoplasmic reticulum stress pathways, disrupting germ cell and Sertoli cell function.[123] In women, heat exposure can suppress the hypothalamic-pituitary-ovarian axis, lower serum estradiol and progesterone concentrations, and disrupt menstrual cyclicity.[12] A prospective study among 631 women with infertility shows that elevated ambient temperatures are associated with premature follicular luteinization and reduced antral follicle count, indicating impaired ovarian reserve.[124] High temperatures induce excessive ROS production, causing DNA damage that compromises embryo viability, blastocyst formation, and implantation potential.[125]

Thermal stress reduces uterine perfusion, leading to placental hypoxia and lysosomal instability, which activates phospholipase A_2 and stimulates prostaglandin synthesis.[35] Prostaglandins contribute to myometrial contractility and cervical ripening, whereas elevated oxytocin concentrations induce rhythmic uterine contractions.[126] Dehydration induced hypovolemia activates the Henry-Gauer reflex, stimulating posterior pituitary release of antidiuretic hormone, which can synergistically amplify uterotonic effects.[127] Extreme heat also impairs placental perfusion and induces localized hypoxia, thereby impairing placental angiogenesis and gas exchange and leading to decidual ischemia and necrosis.[128 129] Furthermore, heat induced systemic inflammation damages trophoblast cells, and activates labor promoting factors such as prostaglandins, collectively increasing the risk of adverse birth outcomes such as preterm birth.[130] Theoretically, elevated temperatures also promote group B *Streptococcus* colonization in the female reproductive tract,[131] and ascending inflammation may collectively increase the risk of infection.[132]

Extreme heat exposure during pregnancy can disrupt maternal thermoregulation, activating the sympathetic nervous system and increasing vasoconstrictive reactivity,[133] which may lead to gestational hypertension.[127 134] This condition can subsequently impair uteroplacental perfusion, resulting in intrauterine growth restriction.[135] Extreme heat may also induce maternal β-cell dysfunction and insulin resistance, elevating the risk of gestational diabetes mellitus by up to 16-20%.[136] Subsequent hyperglycemia is associated with fetal developmental anomalies and infection related complications.[136 137] Overall, extreme heat can disrupt the intrauterine environment via uterine contractility, impaired placental function, and gestational complications, leading to adverse birth outcomes including preterm birth (odds ratio 1.16, 95% CI 1.10 to 1.23), stillbirth (1.05, 1.01 to 1.08),[138] and low birth weight (1.13, 1.04 to 1.23).[139] The mechanistic pathways through which extreme heat exposure contributes to preterm birth have been increasingly well elucidated, as summarized in figure 3.

Musculoskeletal system

Beyond the systemic and organ specific damage described above, extreme heat adversely affects the musculoskeletal system. Dehydration leads to depletion of critical electrolytes, including Na^+, K^+, and Ca^{2+}, disrupting cellular membrane potentials and resulting in neuromuscular dysfunction that manifests clinically as muscle cramps, weakness, and compromised physical capacity.[140] Additionally, heatstroke causes skeletal muscle membrane

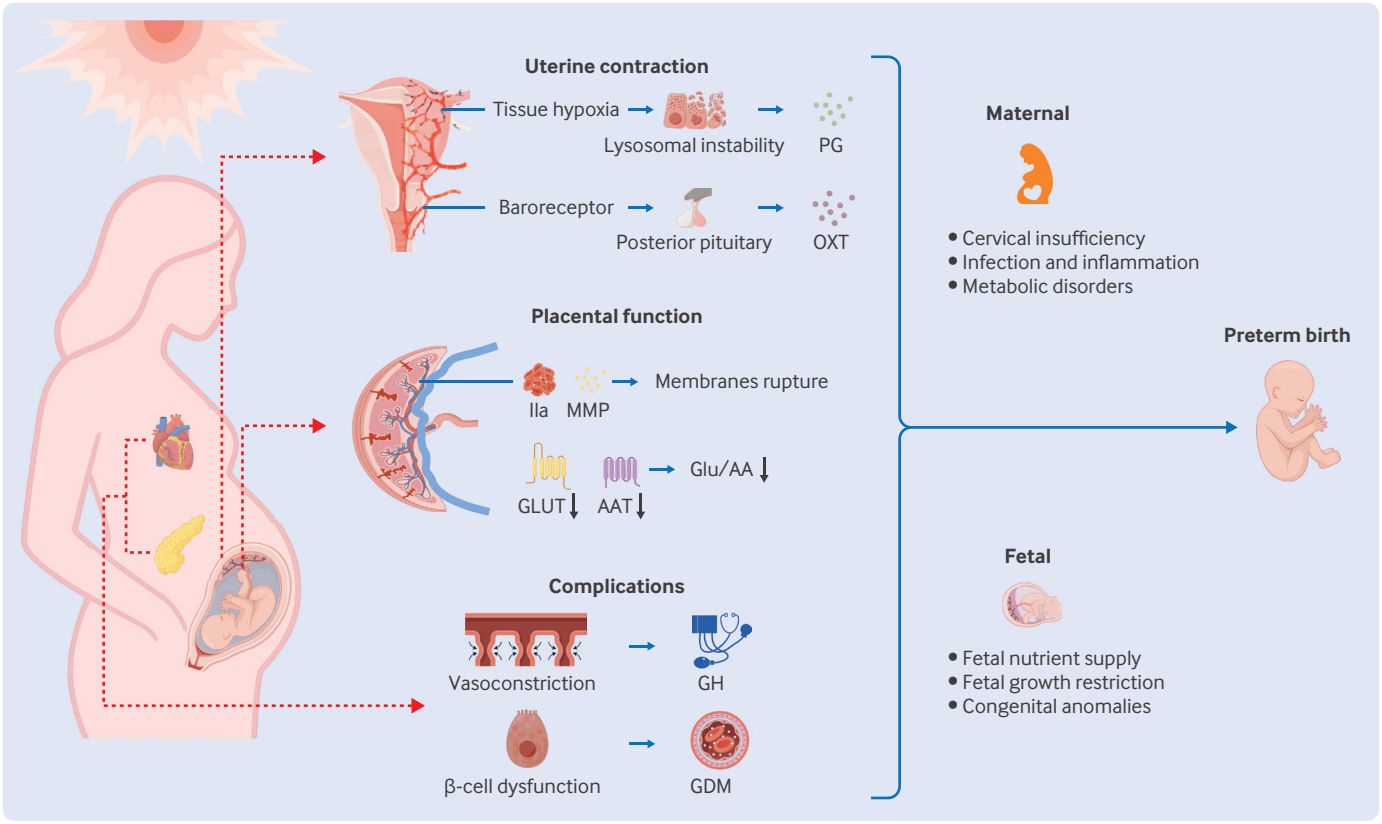


Fig 3 | Mechanistic pathways linking heat exposure to preterm birth. Heat stress can increase maternal concentrations of prostaglandins and oxytocin, enhancing uterine contractility and triggering idiopathic preterm labor. Additionally, heat induced placental hypoperfusion and decidual injury may disrupt placental angiogenesis, resulting in elevated thrombin concentrations. Thrombin can promote the expression of matrix metalloproteinases (MMPs). Through extracellular matrix degradation and compromise of membrane structure, MMPs facilitate the onset of premature rupture of membranes. Heat stress can down-regulate glucose and amino acid transporters such as GLUT8, limiting fetal nutrient supply and inducing intrauterine growth restriction. It also worsens pregnancy complications such as gestational hypertension (GH) and gestational diabetes mellitus (GDM), increasing the risk of medically indicated preterm delivery. These adverse maternal and fetal conditions may collectively amplify pathological processes and increase the risk of preterm birth. AA=amino acids; AAT=α-1 antitrypsin; Glu=glucose; GLUT=glucose transporter; IIa=factor IIa (thrombin); OXT=oxytocin; PG=prostaglandin

damage, subsequently leading to the release of myoglobin and creatine kinase and ultimately triggering rhabdomyolysis.[141]

Skin

Rising extreme temperatures also pose significant risks to skin health.[142] The skin plays a critical role in thermoregulation through vasodilation and eccrine sweating.[143] Miliaria, a common and typically mild heat related disorder, exemplifies direct cutaneous responses to excessive heat.[144] Excessive sweating during heat exposure can lead to skin erythema, maceration, and exacerbation of pre-existing dermatological conditions.[145 146] Elevated temperatures may also promote bacterial and fungal growth, increasing the risk of cutaneous infections and autoinflammatory skin disease.[147 148]

Interconnections

Critically, these multisystem damage mechanisms do not occur independently but through interconnected crosstalk. For instance, heat induced activation of the HPA axis results in elevated cortisol concentrations, which in turn leads to immunosuppression.[149] The enhanced gut mucosal permeability triggers systemic inflammation, further exacerbating other organ injuries.[101] People with CKD are particularly vulnerable to increased cardiovascular strain during heat exposure.[150] Recent evidence suggests that extreme heat exposure may induce epigenetic modifications and DNA damage.[151 152] Specifically, heat exposure in one generation can result in accumulation of risk, increasing the susceptibility of subsequent generations to heat exposure. A randomized crossover trial in 30 healthy adults shows 12 926 CpG sites significantly associated with acute heat exposure, with pathway enrichment indicating predominant involvement in cardiovascular signaling and immune response.[151] A national study among 3686 older adults in the US shows significant associations between heat exposure and accelerated epigenetic aging, a precursor of the morbidity and mortality process.[153 154]

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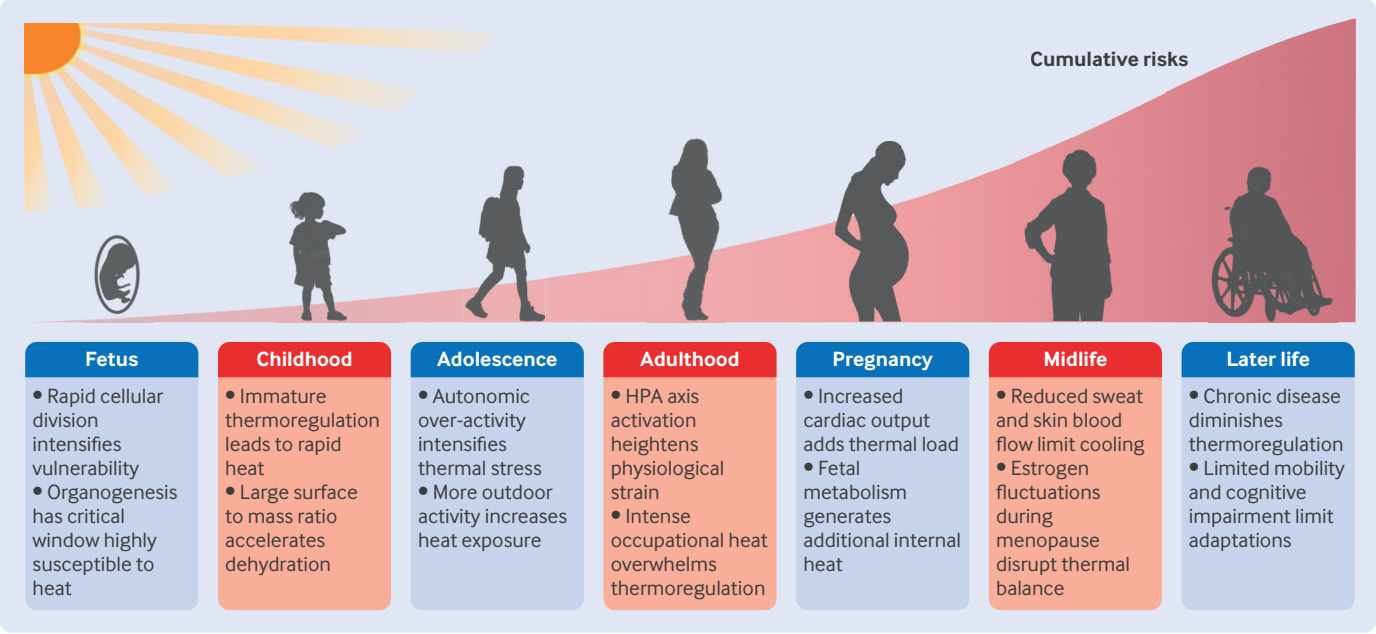

Fig 4 | Susceptibility to heat related health risks from a life course perspective. Extreme heat can affect individuals across all stages of life. This figure illustrates representative stage specific vulnerability factors from the fetal period to later life. HPA=hypothalamic-pituitary-adrenal

Susceptibility of vulnerable populations

Life course vulnerability to heat exposure

As an important environmental contributor, heat exposure affects individuals across all stages of life, with varying vulnerabilities owing to factors including physiological characteristics, behavioral patterns, and social determinants (fig 4). Inter-individual differences in physiological mechanisms across the life course constitute the biological basis of vulnerability.

Prenatal period and infancy

The embryonic and fetal stages represent critical developmental windows, characterized by rapid cellular proliferation and organogenesis, during which increased susceptibility to heat stress occurs.[155] A US multicenter case-control study in 5848 cases of congenital heart defect and 5742 controls associates maternal heat exposure during post-conception weeks 3-8 with increased risk of congenital heart defects.[156] Infants, as a result of immature thermoregulatory systems and higher surface-area-to-mass ratios, absorb more heat and experience a faster rise in body temperature under hot conditions.[157] Although sweating enables some evaporative cooling, it also accelerates dehydration, which is often more severe in infants.[157] Infants' limited ability to communicate or alleviate discomfort without care giver assistance further hampers their heat adaptation capability.[158]

Children and adolescents

Children are more frequently exposed to heat owing to increased outdoor activities, and their underdeveloped thermoregulatory systems make them less capable of coping with thermal stress.[158] Adolescents, likewise, often participate in outdoor activities, and the physiological stress of heat exposure can trigger robust autonomic responses to heat, a key manifestation of which is hyperhidrosis.[12] Beyond physiological effects, heat exposure may also adversely affect adolescents' behavioral and mental health.[159] A European cohort study in 4819 adolescents shows a significant association between cumulative heat exposure and severe attention problems, with a 1.52 (95% CI 0.39 to 2.66) point increase in square-root-transformed attention problem scores at 21.7°C exposure over a two month period.[160]

Adults

In adults, occupational heat exposure is an important contributor to heat related health risks. Outdoor workers, such as construction laborers who constitute 6% of the US workforce, accounted for 36% of occupational heat related deaths from 1992 to 2016.[161 162] In male adults, who predominantly comprise occupational heat exposed groups, androgen associated traits such as sweat rates potentiate the risk of dehydration under humid conditions.[157] Female adults face elevated vulnerability during specific physiological states. During pregnancy, rising progesterone elevates core temperature and, together with increased maternal metabolism and fetal heat production, heightens maternal susceptibility to heat stress.[35] In menopausal women, reduced estrogen impairs heat dissipation by inhibiting cutaneous vasodilation, increasing vulnerability to heat related cardiovascular strain.[163]

Older adults

Among older adults, age related declines in sweat gland function reduce sweating capacity.[157] Chronic conditions and medications further exacerbate vulnerability[157]; for instance, hypertension impairs vasodilation, and diabetes compromises sweating via microvascular dysfunction. Anticholinergic drugs, commonly prescribed to older adults for conditions such as COPD and parkinsonian symptoms, also inhibit sweat gland activity.[164] Additionally, declining physical and cognitive functions, including frailty, mobility limitations, and cognitive impairment, hinder the ability to effectively respond to heat stress. A cohort study from the Chinese Longitudinal Healthy Longevity Survey (2008-18) indicates increased mortality among older people with functional declines in mobility, dependency in activities of daily living, cognitive impairment, and social isolation during heatwaves.[165]

Sociodemographic factors related to heat effects

Sociodemographic factors fundamentally shape heat exposure, response capacity, and underlying vulnerability. People with lower education and income levels often face higher risks of heat related morbidity and mortality.[166] Lower educational attainment is associated with reduced awareness of heat risks and preventive behaviors, and limited income restricts access to essential cooling resources.[167] Ethnic minorities often bear disproportionate burdens owing to intersecting social, economic, and cultural disadvantages. For example, the US historical redlining policies during the 1930s restricted access to mortgages for minority communities, contributing to their concentration in urban heat islands (UHI) with elevated heat exposure today.[168]

As global warming accelerates, populations in temperate and subtropical regions will continue to experience more frequent and severe heatwaves.[169] Although populations in tropical regions may show some degree of physiological adaptation to heat, they remain vulnerable, particularly where infrastructure is insufficient for heat adaptation.[170 171] Rural areas often lack access to cooling resources and healthcare services, whereas urban populations, although benefiting from better infrastructure, are increasingly affected by the UHI effects.[172] Within cities, socioeconomic inequalities are evident: low income communities can experience temperatures up to 5°C higher than wealthier neighborhoods, largely owing to dense housing and limited green space.[3] In slums and refugee shelters, inadequate ventilation, overcrowding, and heat absorbing materials such as corrugated metal roofing further amplify indoor heat exposure.[173]

Synergistic threats

The health impacts of extreme heat are rarely isolated; rather, they are often exacerbated by co-occurring environmental and socioeconomic stressors that are being reshaped by climate change. Understanding synergistic threats is essential for assessing the full spectrum of heat related health burdens, and insights into the biological mechanisms enable a deeper interpretation of environmental co-exposure effects.

Interactions between ambient heat, air pollution, and allergens

Climate change and air pollution are closely interconnected, as fossil fuel combustion, the primary driver of climate change through greenhouse gas emissions, is also a major source of air pollutants.[174] Extreme heat exacerbates ambient air pollution, particularly ground level ozone (O_3) and particulate matter (PM), through enhanced photochemical reactions and stagnant atmospheric conditions.[175 176] Strong evidence shows that extreme heat and air pollution act synergistically to elevate health risks. In India, $PM_{2.5}$ related mortality risk increases from 0.8% at the 75th temperature centile to 4.6% at the 99th centile per 10 $\mu g/m^3$ increase in $PM_{2.5}$.[177] Evidence from Jiangsu province, China, further indicates synergistic effects between heatwaves and $PM_{2.5}$ exposure in triggering deaths from myocardial infarction.[178] A nationwide study in China shows that concurrent exposure to heatwaves and high O_3 concentrations is associated with greater all cause mortality than either exposure alone.[179] However, the interaction between extreme temperatures and air pollution is relatively complex, involving not only synergistic effects but also potential antagonistic mechanisms. For instance, reduced outdoor activity during high pollution episodes may also lessen heat exposure.[180]

Climate change also alters the distribution and concentration of airborne allergens such as pollen and mold.[181] Rising temperatures and elevated CO_2 concentrations not only prolong pollen seasons but also enhance the allergenic potency of pollen.[182] These changes significantly elevate the risk of asthma exacerbations and allergic rhinitis by increasing T cell stimulatory and IgE inducing capacity.[183] On the basis of the summarized evidence, the combined effects of heat, air pollution, and allergens are theorized to disproportionately affect people with pre-existing respiratory and allergic diseases.[60]

Amplification effect of extreme weather events

Other extreme weather events, including heavy precipitation events, floods, storms, droughts, and wildfires, often compound the physiological stress of heat exposure.[184] Floods create stagnant water that fosters pathogen growth and disease transmission, further elevating risks of infectious diseases when followed by extreme heat.[185 186] Additionally, extreme heat increasingly overlaps with wildfire smoke, which releases large quantities of $PM_{2.5}$ and toxic gases.[184 187] A study in California documents synergistic effects between heat and wildfire smoke on daily cardiorespiratory hospital admissions.[187] Prolonged drought intensifies thermoregulatory strain by elevating cardiac workload and electrolyte

depletion.[188 189] Beyond direct health effects, compound drought-heatwaves also trigger secondary disasters, including wildfires and agricultural losses that worsen malnutrition, especially in economically disadvantaged regions.[190 191]

Socioeconomic dynamic changes

Population aging is emerging as a compounding public health challenge and crucial driver for future heat related disease burden.[192] Evidence across 50 countries and regions shows that with 1.5°C, 2°C, and 3°C of global warming, heat related mortality will increase by 0.5%, 1.0%, and 2.5%, respectively; critically, between 20% and 25% of these deaths can be attributed to population aging.[193] Additionally, the accelerating pace of urbanization amplifies the UHI effects.[194 195] Industrial restructuring, as well as contributing to climate change mitigation, also introduces new environmental and health challenges associated with the development of emerging energy technologies.[196]

Initiatives to reduce negative health outcomes due to heat exposure

Adaptive capacities also mediate heat related health risks, shaping outcomes at both individual and community levels. Initiatives to reduce health risks posed by extreme heat exposure range from the adoption of individual cooling strategies through to community interventions and public policies.[167] This section outlines the characteristics of widely implemented individual heat adaptation measures and community interventions, particularly those targeted at at-risk populations.

Individual adaptation measures

Individual adaptation measures primarily focus on enhancing knowledge about heat health and facilitating practical adaptation behaviors.[197] These measures vary in their affordability and effectiveness and may not be beneficial in certain conditions. For instance, although the use of electric fans can reduce heat strain and improve thermal comfort, these devices accelerate body heating and increase physiological heat strain when used at temperatures above 45°C with low humidity.[167] The use of air conditioning is effective at promoting thermal comfort, but the cost of operating these units is an important barrier, particularly for older people, socioeconomically disadvantaged people, and those living with disabilities.[198 199] The use of ice towels and similar devices reduces heat strain, but they can become ineffective within 30 minutes as the ice melts. For the treatment of heatstroke, clinical guidelines recommend active cooling methods, especially cold water or ice water immersion to achieve the fastest cooling rate.[200] Animal studies also show that rapid cold fluid infusion improves organ function and prognosis in rats with classic heatstroke by preserving cardiac and renal function.[201] Self-pacing and taking regular breaks from work can be an effective strategy to reduce metabolic heat production and lower body temperature, particularly in situations where other cooling strategies cannot be implemented.[167]

Community based interventions

Community interventions range from population-wide policies and guidelines, such as heatwave early warning systems operationalized at city, state, or country level, through to targeted, localized initiatives, such as occupational safety policies and healthcare system preparedness. These are discussed in the sections below, with specific examples, strengths, and limitations summarized in table 1.

Heatwave early warning systems

Heatwave early warning systems are widely implemented globally to provide communities with advanced notice of predicted heatwaves on the basis of location specific temperature thresholds, along with the communication of graded alerts, enabling timely implementation of adaptive measures.[197 214 215] Elements of such systems that contribute to their effectiveness include components of heat health action plans, such as the use of media announcements to warn, targeted messaging for at-risk groups, and daily outreach with pre-identified vulnerable individuals throughout the heatwaves.[202]

Community heat health action plans

Heat health action plans involve the delivery of targeted education, prevention, and adaptation measures at different levels, ranging from community groups and organizations to local and national governments.[204 210 214 216] Often integrated with or triggered by heatwave early warning systems, these plans emphasize raising awareness of heat related health risks through targeted health education, encouraging protective behaviors. A 2021 scoping review indicates that heat health action plans incorporating multiple components such as heat monitoring systems, information campaigns, and surveillance and management of individuals with identified vulnerabilities are highly effective in reducing heat related mortality and morbidity, particularly among at-risk populations.[217]

Occupational health and safety policies

To reduce the risk of heat related injuries and illnesses among outdoor workers, occupational health and safety policies may include targeted guidance on working safely in high temperatures. A 2017 review of Australian policies emphasizes the need for such guidance to be informed by location specific research on the effects on physical and mental health of occupational heat exposure, characteristics of vulnerable worker groups, and meteorological thresholds associated with adverse outcome.[208] Furthermore, heat health guidelines and policies should account for occupation specific factors, such as the use of uniforms or personal protective equipment that may impede heat dissipation.[199] To enhance accessibility, especially among workers

Table 1 | Examples, strengths, and limitations of community based interventions to reduce health risks associated with heat exposure

Interventions	Examples	Implementation	Effectiveness	Strengths	Limitations
Heatwave early warning systems	Comprehensive heatwave early warning system implemented in Adelaide, South Australia[202]	Implemented in November 2009. Involves collaboration between the state Department of Health, Bureau of Meteorology, and South Australian State Emergency Service to enable surveillance, issuance of early warnings of upcoming heatwaves, and provision of heat health messages through a range of channels including mass media and social media	Significant reductions in ambulance callouts for cardiac and renal problems and heat related emergency presentations during a heatwave following implementation of the South Australian warning system[202] Cost effectiveness, with the South Australian system having a benefit-cost ratio of 2.0-3.3, contributed to by marked reductions in healthcare costs[203]	Cost effectiveness, enhanced community and service provider preparedness, wide reach due to involvement of government agencies and communication through mass media channels[202]	Requires ongoing coordination, collaboration, and engagement across multiple agencies, including meteorological organizations, government departments, and emergency services[202]
Community heat health action plans	Five local government heat health action plans in Honshu, Japan[204]	Honshu action plans are based on real time monitoring of local weather conditions, with predefined thresholds triggering activation of automated warning messaging via several communication channels (eg, email and text messaging)[204]	The Honshu heat health action plans were found to be resource and labor efficient and were informed by local needs and resource availability[204]	Heat health action plans have been found to be effective, highly feasible, and sustainable as a result of being tailored to local community needs and resource availability[204 205]	Some action plans require individuals to register to receive warning messages,[204] meaning they may not reach socially isolated community members, whereas others rely on local volunteer networks to play a key role in information dissemination and active outreach,[204] potentially reducing the long term sustainability of these initiatives
	Heat action plan in Ahmedabad, India[206]	Ahmedabad heat action plan was implemented in 2014. The plan includes the issuance of progressively more urgent alerts and warnings based on local temperature thresholds. Warnings trigger the activation of community outreach and interagency preparedness and response activities[206]	Implementation of the Ahmedabad action plan was found to reduce all cause mortality rates during the summer months, with the largest declines observed during periods of extreme heat[206]		
	Grassroots awareness program in Odisha, India[205]	The Odisha awareness program is focused on communicating practical actions, strategies and "dos and don'ts" at the community level to reduce the negative health consequences of heatwaves[205]	The Odisha awareness program positively contributed to reducing mortality due to heatstroke[205]		
Occupational health and safety policies	Multifaceted intervention for outdoor power grid industry workers in Chongqing Municipality, China[207]	Implemented in 2022 in urban and suburban outdoor work sites. The intervention incorporated targeted measures including app based education, educational posters, risk monitoring, and personal protective equipment for prevention of heat related illnesses[207]	The Chongqing Municipality intervention was found to reduce the risk of occupational heat related illnesses and improve use of personal protective equipment among outdoor workers[207]	Targeted workplace education and guidelines can promote protective behaviors such as appropriate work-rest ratios and adequate hydration. Appropriate uniforms and personal protective equipment can improve sweat evaporation and reduce heat retention[167]	Interventions incorporating heat health education may not be suitable for workers with low literacy, unless they are made available in a range of accessible formats.[208] Workplace requirements to work during specific hours or to wear prescribed uniforms or personal protective equipment may limit the extent to which guidelines can be followed by some workers[167]
Healthcare system preparedness	The Greater New York Hospital Association's Sit Stat platform in New York, USA[209]	The Sit Stat regional situational awareness and information sharing platform is a key component in coordinating emergency responses. Critical information is shared by established secure communication channels between member hospitals and relevant government agencies to inform response efforts[209]	Sit Stat includes information about key contacts, services, and capabilities for each facility and has been used to rapidly collect and disseminate information on operational impacts and needs during extreme heat events, thus improving efficiency[209]	Adequate preparedness can reduce strain on scarce health system resources, enhance triage and treatment protocols, and improve patient outcomes[209 210]	Healthcare system preparedness efforts can be limited in scope. Enhancing healthcare system preparedness should include consideration of potential vulnerabilities of communication, energy, and water and waste management systems to enhance their resilience to extreme heat[167 209 210]
Infrastructure and resources	Cooling centers in Maricopa County, Arizona, USA[211]	Cooling centers were implemented in existing publicly accessible buildings and involved the provision of services, including an air conditioned environment, water, and amenities such as internet access and toilets, to more than 1500 visitors daily[211]	An evaluation of 53 Maricopa County cooling centers found that their location within existing community, senior, or religious centers positively contributed to their cost effectiveness and sustainability[211 212]	Cooling centers have relatively low implementation and maintenance costs. The use of existing community spaces enhances the uptake of these services	Some cooling center locations incurred additional costs while operating, primarily owing to additional staff hours, bottled water purchases, and higher utility bills[211]
	Green infrastructure initiatives in European cities[213]	The European green infrastructure initiatives were primarily focused on increasing urban tree canopy cover, involving multisectoral collaboration between government agencies, community organizations, and businesses[213]	A health impact assessment of 93 European cities estimated that increasing urban green infrastructure to bring urban tree coverage to 30% could prevent 2644 premature deaths during the summer months[213]	Green infrastructure, including increasing tree canopy cover, reduces surface temperatures and promotes cooling via evapotranspiration from leaves and evaporation from soil[167]	Green infrastructure initiatives often require higher initial financial investment, as well as ongoing maintenance costs.[167] Additional challenges include poor compatibility with existing urban infrastructure and space constraints

with limited literacy, materials should be available in multiple formats and languages.[208]

Healthcare system preparedness

Healthcare system preparedness must be guided by local heat vulnerability assessments, with a focus on at-risk populations such as those with chronic conditions, rural and remote residents, and low socioeconomic groups, to ensure allocation of appropriate staffing and resources that meet community specific needs, equity, and cultural acceptability.[209 210] Additionally, systems for coordinated information and resource sharing before, during, and after extreme heat events should be strengthened to enhance readiness, response, and collaboration among healthcare providers, first responders, and government agencies.[209]

Infrastructure and resources

Examples of infrastructure and resource allocation initiatives to reduce the negative impacts of extreme heat include cooling centers, which are particularly critical for at-risk populations, such as individuals experiencing homelessness and those without air conditioning at home.[212] Additionally, urban planning initiatives focusing on green infrastructure such as cool roofs, green walls, and urban forests mitigate UHI effects and enhance climate resilience, providing lasting environmental, social, and health benefits and contributing to reductions in heat related risks.[213]

Recommendations for health professionals and clinical management

Managing acute heat related illnesses

Global warming exacerbates health risks, necessitating enhanced preparedness of clinicians for heat sensitive conditions, especially acute heat related illnesses.[218] The documented gaps in knowledge about climate health among healthcare service providers[219-221] make the rapid recognition and management of these conditions all the more urgent. Clinicians, particularly emergency physicians, should proficiently distinguish between heat cramps, heat exhaustion, and heatstroke. Early identification of heatstroke, characterized by a core body temperature exceeding 40°C, central nervous system dysfunction (such as confusion, seizures, or coma), and multi-organ involvement, is crucial.[222 223] Prompt evidence based cooling within the "golden 30 minutes" is essential to control core temperature, stabilize circulation, and maintain organ function.[200 219] The routine use of paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs (NSAIDs), or salicylates to lower body temperature in patients with heatstroke is discouraged.[200] Concurrently, rapid assessment and management of complications, including rhabdomyolysis, disseminated intravascular coagulation, AKI, and cerebral edema, are vital, along with continuous monitoring of multi-organ function.

Effective management requires a coordinated multidisciplinary response involving emergency medicine, intensive care, nephrology, neurology, and other relevant specialties. Given the complexity and variability in managing heat sensitive conditions, such as cardiovascular and renal disorders, treatment strategies must be meticulously tailored to account for individual pathophysiology and comorbidities. Understanding the pathophysiology and epidemiology of acute heat related illnesses enables clinicians to provide targeted prevention advice.[220-222]

Integrating heat exposure into disease risk assessment

Beyond acute symptoms, clinicians can consider integrating heat exposure as a potential environmental risk factor into chronic disease management frameworks. Systematically assessing the possible contribution of heat exposure to disease progression may be helpful, particularly among vulnerable populations. During consultations with patients, heat exposure history can be routinely incorporated into clinical assessments, encompassing environmental conditions such as access to cooling and housing insulation,[167] behavioral patterns such as engagement in heat intensive activities, and quantitative exposure characteristics including temperature thresholds and duration of exposure.[223] Such assessments are particularly valuable in managing heat sensitive conditions such as cardiovascular, respiratory, urinary, and mental health disorders.[45 224 225] Incorporating these assessments into electronic health records and clinical workflows can support the development of personalized heat health management, including tailored advice on activity modification, hydration strategies, and preventive care.

Adjusting drug therapy during hot weather

Clinicians should consider the effect of heat exposure on both drug therapy and the management of heat sensitive illnesses. Many drugs used for chronic diseases, including antidepressants and cardiovascular drugs, may impair thermoregulatory capacity.[221] Therefore, adjustments in the timing of administration may be necessary. Particular attention should be given to diuretics, which can worsen dehydration and may be warranted during heatwaves to prevent metabolic complications.[226 227] Nephrotoxic agents, including NSAIDs and aminoglycosides, may also pose increased risks under heat induced dehydration.[228] However, recognizing the potential challenges is important, as inappropriate changes may lead to adverse effects such as blood pressure instability or electrolyte imbalances.

Pharmacological modifications should be guided by individual assessments, the status of disease control, and available healthcare resources. Clinicians should enhance medication counseling

Box 1: Developing a thermosensitive clinical biomarker profile

Thermosensitive biomarker profiles offer critical insights into heat induced subclinical pathology, enabling early detection of pathological alterations before overt clinical manifestations. For example, cardiovascular specific markers including hemoconcentration indicators such as elevated hematocrit and serum osmolality provide evidence for volume depletion. Beyond diagnostics, biomarkers aid in identifying vulnerable individuals, as shown by endocrine disturbances such as abnormal thyroid hormone concentrations that compromise thermoregulatory function. Furthermore, dynamic biomarker monitoring may guide precision interventions.[238 239] Therefore, heat sensitive biomarkers may inform future clinical guidelines in diagnosis, risk stratification, and treatment.[48] Notably, the development of reliable thermosensitive biomarker profiles should account for inter-individual variability and confounding factors, such as diurnal rhythms and psychological stress, which can influence biomarkers such as cortisol and compromise the specificity of heat related responses. Balancing sensitivity and specificity across diverse populations remains a key challenge.

and implement personalized treatment under clinical supervision, including predefined dose modification protocols triggered by heat warnings or symptoms.[221 229] A stratified approach is recommended, with individualized medication adjustments in settings with robust healthcare capacity and a focus on non-drug interventions, such as cooling strategies and health education in areas with limited medical infrastructure. In addition, comprehensive patient education is essential, covering recognition of symptom exacerbation, adherence to hydration strategies, effective cooling methods, and specific medication precautions during heat exposure.

Guidelines

The Society of Critical Care Medicine provides acute clinical guidance for heatstroke, outlining cooling modalities and drug treatments.[200] Preventive recommendations from the European Society of Cardiology and the American College of Obstetricians and Gynecologists highlight the effects of climate change on cardiovascular and maternal-fetal health, emphasizing population level interventions.[230 231] The World Health Organization provides broader guidance on climate change and health, focusing on systemic, large scale strategies.[232] Additionally, government issued occupational heat exposure guidelines provide practical preventive measures.[233]

Although existing guidelines show strengths in heatstroke and targeted prevention, few clinical guidelines provide evidence based recommendations on other heat related health risks, with a notable lack of standardized protocols for heat adaptive care.[234] This gap is evident in fragmented risk assessments, absent adjustment protocols for high risk medications, and non-standardized education materials. To reduce these limitations, clinical guidelines should establish clear criteria for identifying vulnerable populations, integrate heat exposure into routine clinical assessments, and include specific strategies for managing heat sensitive conditions.[35] Key implementation steps include providing adapted patient education on cooling strategies and establishing guidance for drug dose adjustment during extreme heat.[221] Additionally, passive heat acclimatization strategies, such as intermittent heat exposure and exercise induced acclimation, may serve as valuable tools to enhance physiological resilience, particularly among workers regularly exposed to high heat environments.[235-237]

Emerging treatments

Emerging treatments under investigation include advanced cooling methods, such as ice water immersion (1-5°C) or cold water immersion (9-12°C), which are recommended when feasible for rapid core temperature reduction.[200]

Limitations of this review

Several limitations should be considered. Firstly, this review is not a systematic review; study selection prioritized recent, high impact publications on the basis of thematic relevance and methodological quality, which may result in the omission of some relevant studies. Secondly, the definition of "extreme heat" varied across the included studies, with no unified threshold. Epidemiological findings should be interpreted cautiously owing to heterogeneity in definitions of exposure, modeling approaches, and population vulnerability. Additionally, mechanistic insights derived from animal studies have inherent limitations in translational applicability to humans. Finally, although the proposed thermosensitive biomarkers and clinical recommendations represent promising future directions, they remain exploratory and warrant further validation as well as detailed implementation studies.

Conclusions

This review highlights the profound effects of extreme heat exposure on multisystem physiological dysfunction and increased disease burden. Crucially, these mechanisms are interconnected, with effects manifesting through complex, inter-related pathways. A deeper understanding of the multisystem damage mechanisms linking heat exposure to health risks is essential for protecting vulnerable populations across the lifespan. Future climate change is expected to intensify extreme heat events, leading to shifts in the overall disease spectrum and reshaping the global disease landscape. As well as acute heat

GLOSSARY OF ABBREVIATIONS

- AKI—acute kidney injury
- CKD—chronic kidney disease
- COPD—chronic obstructive pulmonary disease
- HPA—hypothalamic-pituitary-adrenal
- NSAID—non-steroidal anti-inflammatory drug
- RAAS—renin-angiotensin-aldosterone system
- RCP—representative concentration pathway
- ROS—reactive oxygen species
- TNF-α—tumor necrosis factor-α
- UHI—urban heat islands

QUESTIONS FOR FUTURE RESEARCH

- What are the temperature and duration thresholds for the long term cumulative effects of recurrent heat exposure on the progression of chronic diseases, such as chronic kidney disease, neurodegenerative diseases, and cardiovascular dysfunction?
- What are the precise molecular and cellular mechanisms underlying the crosstalk between multiple systems (eg, gut-brain axis, gut-liver axis, renal-cardiovascular axis) during heat stress, and how do these interactions amplify systemic damage?
- How can heat health warning systems be integrated with electronic health records to automate risk alerts and guide targeted interventions for vulnerable individuals?
- How can integrated, evidence based protocols, encompassing drug therapy adjustment and passive heat acclimation, be developed and implemented to deliver personalized interventions?

related illness, a clear shift toward higher incidence and mortality from other heat sensitive diseases is to be expected.

Enhanced clinical awareness and preparedness are critically needed to confront the complex health effects of heat exposure. To tackle this escalating public health crisis, evidence based guidelines should urgently establish standardized heat resilient clinical protocols, integrating both prevention and treatment. Furthermore, incorporating thermosensitive biomarkers into risk assessment and diagnostic frameworks may offer a promising approach for early detection and personalized interventions, enabling clinicians to identify people at risk and tailor treatments accordingly (box 1). Bridging the gap between mechanistic understanding and clinical practice is critical to mitigate the health risks of extreme heat in a rapidly warming world.

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