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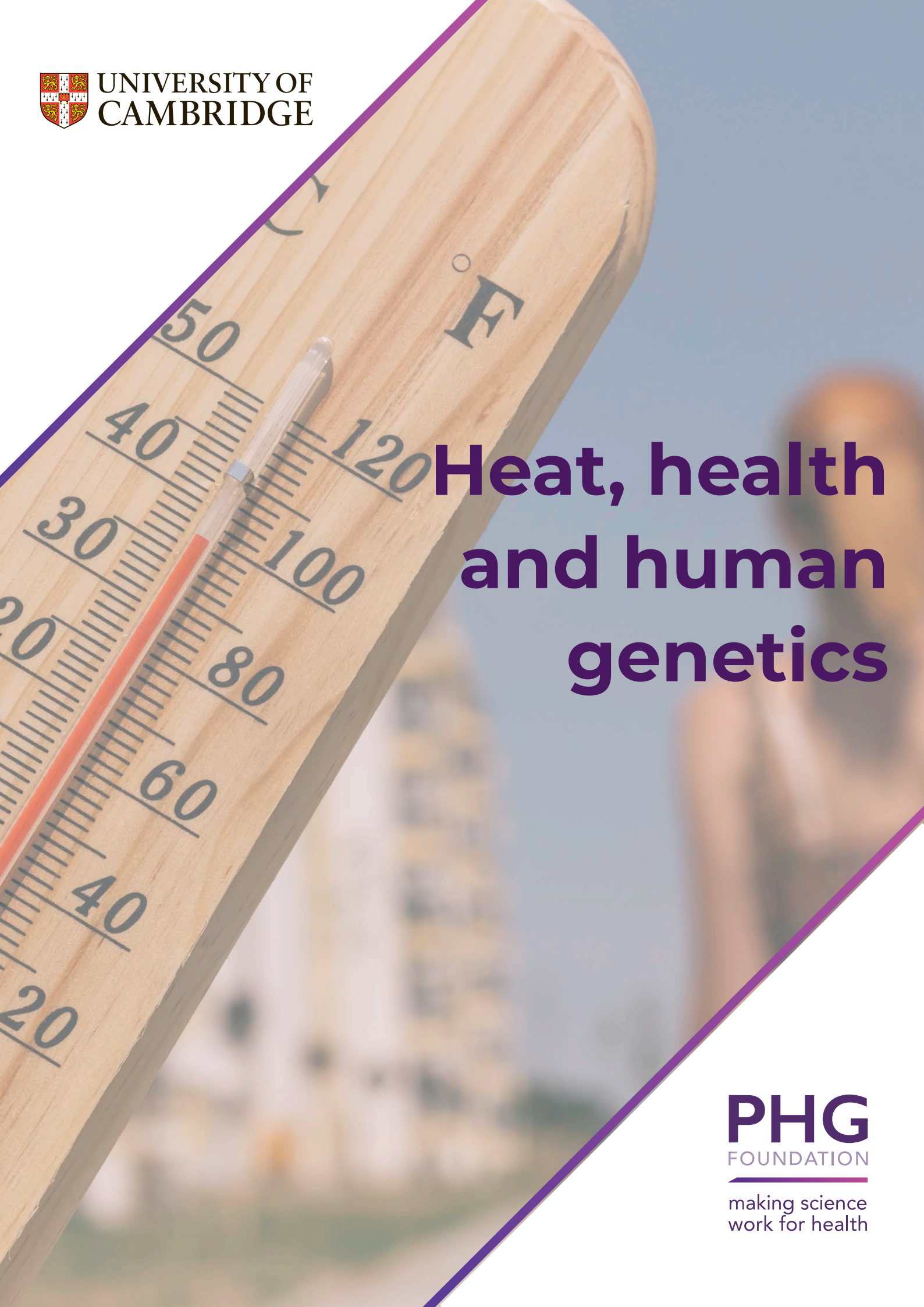

Heat, health and human genetics

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making science work for health

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About this report

Climate change is exacerbating existing risks to human health and creating new ones. This report looks at the potential impact of climate change on human health, particularly focusing on increasing temperatures and episodes of extremely high temperatures, i.e. heatwaves.

We will explore heat response as well as the underlying genetic basis of heat-related conditions and illnesses, and how this information could have utility in improving human health, for example in populations experiencing extreme environmental heat conditions.

In this report we:

- Describe the future health risks from environmental exposures associated with climate change, given changing and increasing climatic temperatures
- Describe heat associated health risks, how the human body responds to heat and current understanding of the threat of heat to health
- Assess the current level of evidence of the role of genetic variation in environmental heat response, and the nature of the research that has been conducted
- Outline potential ways in which genetic information on heat response could be applied to help manage the future health burden associated with climate change heat

Key points:

- Maintaining the body's temperature (thermoregulation) is necessary to the healthy functioning of the human body. It is a complex function, that involves a number of different biological processes
- Climate change is increasingly exposing humans to extreme environmental temperatures
- Exposure to extreme heat can result in adverse health outcomes. Some effects are immediate while others may be delayed
- Research on how the human body responds to environmental heat is gaining importance as exposure becomes more common
- Understanding of human responses to heat is currently limited owing to the complexity of the topic
- There is little genetic research in human thermoregulation and the impact of environmental heat exposure
- Research in genetics and genomics could provide important insights
- This report identifies reasons to support coordinated programmes of research to investigate this increasingly important threat to health

Climate change and illness

- Climate change
- Warming climates

1.1 Climate change

Climate change is exacerbating existing risks to human health and creating new ones. Whilst some health risks from climate change are indirectly linked to a changing climate e.g. crop failure in drought leading to famine and malnutrition, others are direct results of exposure to environmental hazards.

Examples of direct risks

- Rising temperatures due to global warming resulting in increased illness and death from heat related conditions
- Increased amounts of flooding posing a risk of drowning as well as exposure to waterborne diseases

Examples of indirect risks

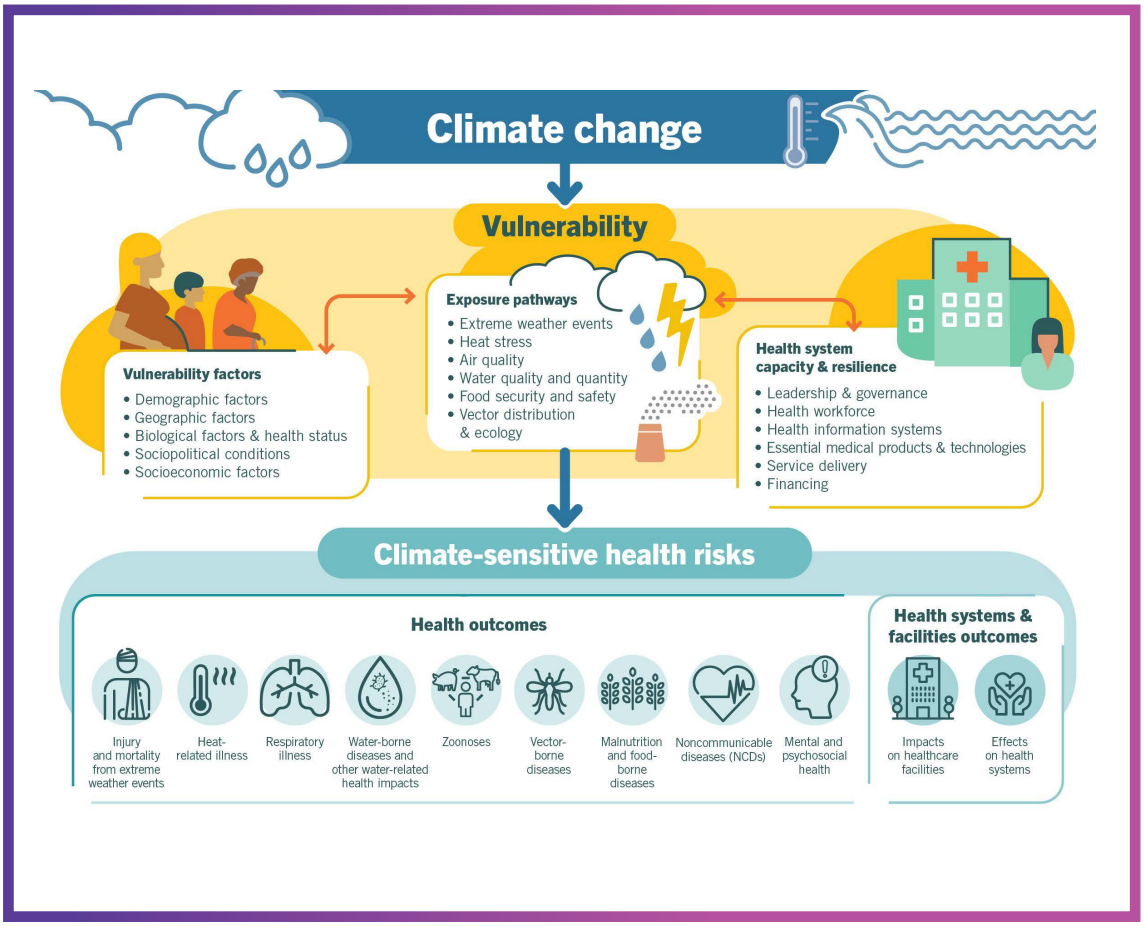
- Droughts and crop failure resulting in water and food shortages
- Deterioration of air quality due to increased fires, dust and air pollution in arid conditions, exacerbating diseases affecting the respiratory and cardiovascular system
- Shifts in the distribution and numbers of pathogens, as factors including temperatures and water level change create new and/or increased health threats from infectious disease

The World Health Organization (WHO) now views climate change as the biggest health threat facing humanity. Whilst climate change is already having an impact on human health in some parts of the world, between 2030 and 2050 the WHO expects climate change to cause an additional 250,000 deaths per year from malnutrition, malaria, diarrhoea and heat stress alone.

As outlined in Figure 1, the impact of climate change is not just influenced by the existence of an environmental hazard, but by a variety of factors affecting the vulnerability of specific populations and individuals to the environmental hazard.

One of the main climate change associated risks with a direct impact on human health is increasing temperatures with periods of hazardous levels of heat. This will be the subject of this report.

Figure 1: An overview of climate-sensitive health risks, their exposure pathways and vulnerability factors. Climate change impacts health both directly and indirectly, and is strongly mediated by environmental, social and public health determinants. (WHO, 2021) [1].



1.2 Warming climates

Climate change is increasing the frequency, duration, intensity, timing and spread of extreme heat across the globe. Combined temperature and humidity extremes already exceed human biophysical tolerance in some locations.

Temperature extremes, especially humid heat, are increasing with once rare record-breaking heat events becoming more common. An extra 475 million exposures to heatwaves (that is, one person experiencing three days or more of extreme heat) were observed globally in 2019 compared with 1986-2005 [2].

Clear evidence links the intensity and frequency of heat extremes to human induced global warming, which also increases the probability of compound events such as concurrent heatwaves and droughts.

The implications are serious as extreme heat has a substantial impact on all 17 UN sustainable development goals—including zero hunger, good health and wellbeing for all, climate action, and reduced inequalities.

Global urban exposure to extreme heat is changing as a result and has increased nearly 200% between 1983 and 2016, affecting 1.7 billion people (23% of the planet's population) [3]. Spreading urbanisation in this period can explain some of this increase. Urban areas experience thermal storage, where heat is stored in building materials (cement, asphalt, steel) during the day which is then released at night time – also known as the heat island effect [4].

Regions that are currently most affected by extreme heat include South Asia, West Africa, Central America (including Mexico and the Caribbean), Middle East and Southeast Asia [3]. Climate change scenarios indicate that extreme events are expected to increase in the future, including into regions where heatwaves are not currently frequent.

Heatwaves are episodes that are defined by taking into account both temperature and humidity levels during the day as well as high night-time temperatures [5]. Their frequency and occurrence are increasing (Figure 2).

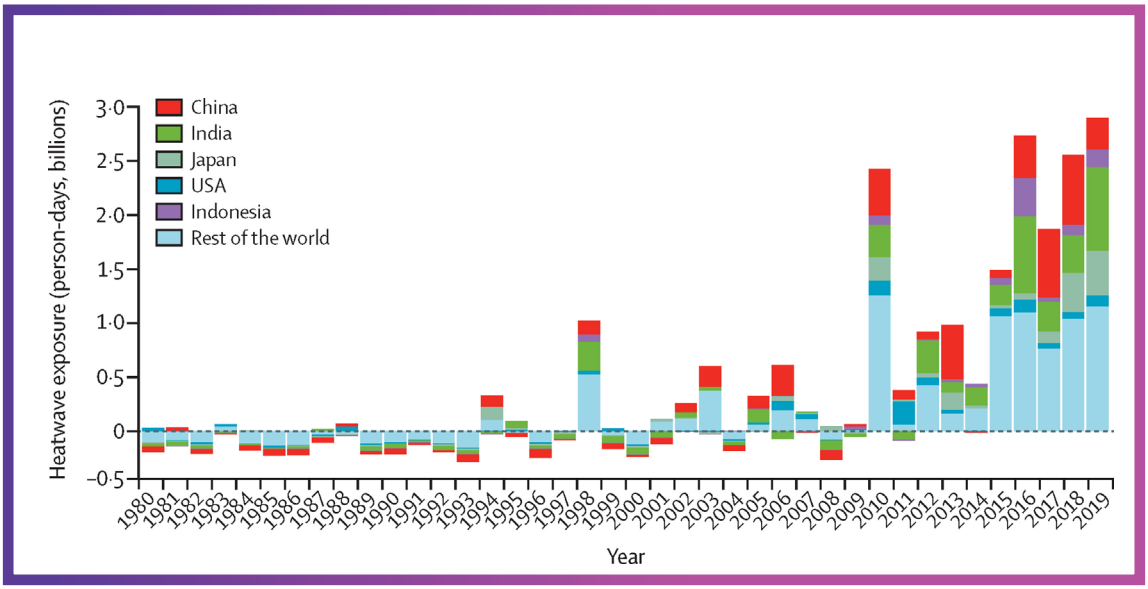
What is considered abnormally high will differ according to the average high temperatures for a country or region. For example, in England, days on which the mean Central England temperature is greater that 20°C are classified as a heat period.

Periods of extreme heat can be endured by the human body, though only for a few hours and with considerable time needed for recovery. Heatwaves are acute and can last for several days, generally there can be reprieve and recovery periods such as cooler temperatures at night. However, as average night-time temperatures are also predicted to rise as well as urban areas being heat islands, there is a reduction in the reprieve and recovery time from high temperatures.

This means people will potentially need to sustain a thermoregulatory response over several days. The body's thermoregulatory response can impact health after one day of extreme heat and is likely to be more devastating if raised temperatures last for a several days, even if they are less extreme. Even relatively mild heat waves can be deadly when they occur in places where people are not prepared for these temperature fluctuations.

Currently, the most common method of heat exposure monitoring involves the assessment of environmental parameters, such as natural wet bulb temperature, global average temperatures and 'normal' dry bulb temperature.

Figure 2: Change in days of heatwave exposure relative to the 1986–2005 baseline in people older than 65 years [6].



Wet-bulb temperature (TW) is the temperature read by a thermometer bulb that is covered in a cloth soaked in ambient temperature water, over which air is passed. Water evaporating from around the bulb has a cooling effect. The higher the humidity of the surrounding air, the less moisture can escape and the higher the wet-bulb reading will be. It will always be lower than the actual temperature, until the air is completely saturated with moisture vapour.

The use of TW from a climatology and meteorology perspective has only begun recently but the importance of this measurement for human health has become clear [7].

As TW takes humidity into account when measuring surface temperatures, it is a useful way to assess the risk to human health rather than air temperature alone. Humans sweat to cool off, but sweat will evaporate more slowly in more humid conditions, meaning that cooling down will also be slower. This causes the internal body temperature to rise.

Moderate risk for heat illness begins around TW of 29°C, with extreme risk above 32°C TW. For context, 29°C TW could occur at 29.1°C air temperature in 99% humidity, or at 50°C air temperature in 19% humidity. If the TW exceeds 35°C for an extended period, people are at risk of hyperthermia/heatstroke which can be fatal. At this temperature human bodies switch from shedding heat to the environment, to gaining heat from it.

Increasing numbers of heatwaves have persistently high TW, with not only high heat levels but also high humidity. The temperature threshold beyond which the human body cannot survive - a TW of 35°C - is increasingly being seen in some parts of the world [7]. There is also increased sustained exposure to high average temperatures, with areas having TW over 33°C.

Heat associated health risks

- What is a dangerous amount of heat?
- Human response to heat and the associated health risks
- Who is at risk?
- Understanding the management of heat for health

2.1 The effect of heat on population health

Hot weather and heat extremes impact human health [8]. This mainly is a result of the human body not being able to regulate core body temperatures, meaning that the greatest impact is in populations that are unable to thermoregulate efficiently, such as the elderly or very young.

First we will look at what a dangerous temperature is, how the human body responds to heat, and then the impact that response has to the human body and heat illness. Then the effect on human populations will be explored from who is at risk, as well as morbidity and mortality rates. Finally will look at understanding the ways in which we can manage exposure to heat for health purposes.

2.2 What is a dangerous amount of heat?

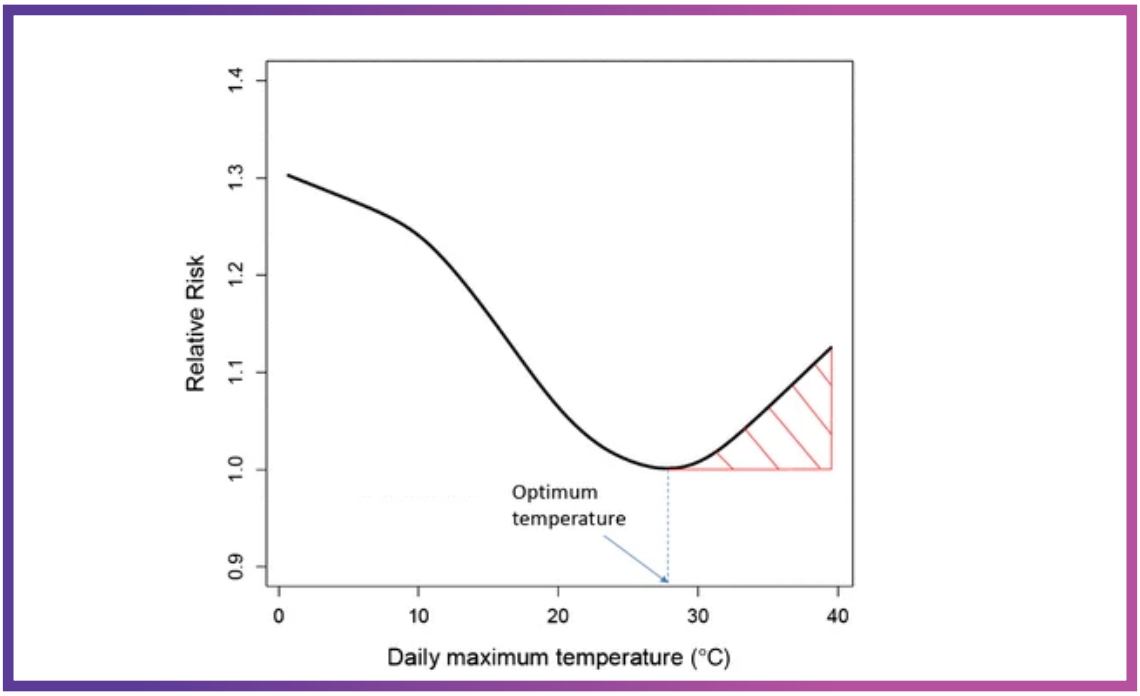
During periods of abnormally high temperatures, mortality rates increase. However, what is an abnormally high temperature for one region may not be considered high for another - excess deaths can occur regardless of the absolute temperature.

For most populations, there is typically a V-shaped relationship between environmental temperature and mortality (Figure 3). For any region around the world, the optimum environmental temperature at which mortality is lowest is approximately the 84th percentile of the daily maximum temperatures a population is exposed to [14].

Excess mortality occurring at environmental temperatures above the optimum temperature can be attributed to 'heat'. This means that for individuals in the USA the optimum temperature for those living in Phoenix is ~41.7°C, whilst for those in Seattle it is ~22.2°C. In the UK temperatures above 20°C may be considered high.

For example, 3,271 excess deaths occurred during five heat periods in England between June and August 2022, when mean Central England temperatures rose above 20°C and/or when heat health alerts were issued [15] (Box 1). According to one report, the number of heat-related deaths in the UK could increase to 7,040 deaths per year by 2050 [16].

Figure 3: Heat-related relative risk of excess mortality, shown by the shaded area, for Tokyo Prefecture for 1972–2008 [14]. The optimum temperature will vary between regions and relates to the daily maximum temperature of the location.



Box 1. Excess deaths during Summer 2022 in England and Wales

In England there were five heat periods that occurred between June and August 2022, defined as days on which the mean Central England temperature was greater that 20°C and/or on which a Level 3 Heat Health Alert was issued [15]. Across all these periods 3,271 excess deaths were seen, 6.2% above the 5-year average. Most excess deaths occurred within the second heat period (10th-25th July) at 10.4% above the average.

These excess deaths did not occur equally across all age groups: the elderly were most vulnerable with 5,017 excess deaths in those aged 70 years and over, whereas younger age groups showed below average mortality by 1,749 deaths. The death rate also fell to below average following each period, suggesting that the deaths of already vulnerable individuals had occurred sooner due to the heat [15]. There were more excess deaths observed in females (2,129) than males (1,116), a reverse trend to that normally seen.

This evidence suggests it is the degree of change in temperature from the average rather than absolute temperature values that contributes to excess deaths in a population. Also, environmental heat levels do not necessarily correlate with actual individual exposure levels.

A range of factors will affect a population's ability to cope with heat. This includes infrastructure to avoid the heat altogether, which will be affected by economic factors, and behaviours to cope with and avoid heat. For example, in areas accustomed to high average temperatures, air conditioning and fans may be easily accessible. However, once exposed to a particular level of heat, an individual's biological ability to respond and thermoregulate will ultimately affect their risk of heat related illness and mortality.

There are a range of biological mechanisms underlying heat related illness and the demographics and biological characteristics of a particular population can influence its levels of heat related morbidity and mortality.

2.3 Human response to heat and the associated health risks

Temperature is a critical variable in human health. Humans possess a variety of biological thermoregulatory mechanisms designed to maintain core temperature, which ranges from 36.1°C to 37.2°C, to within a couple of degrees, regardless of the external environment temperature. Core temperature varies between individuals and can be influenced by age, activity, and time of day. For example, during strenuous exercise, core temperature can rise temporarily to as high as 40°C. Responses to increasing core body temperatures, through thermoregulation, occur due to rising external temperatures and/or normal metabolic processes within the human body.

Thermoregulation

To cope with excess heat, humans have a sophisticated cooling system that includes bipedal locomotion, naked skin, and sweat glands [7, 17]. Thermoregulation to maintain a stable body temperature is a complex process that involves the circulatory, nervous and respiratory systems. Thermoregulatory features aim to restore normal body temperature by enabling important physiological changes to occur in response to high temperatures, which are further amplified by humidity [2]. For example:

- Blood flow redistribution to the skin, known as cutaneous vasodilation, takes place
- Sweating increases
- Changes occur in the renal system to maintain fluid and electrolyte balance
- Adjustments occur to maintain optimal body temperature in the:
    - Circulatory system (such as vasodilation)
    - Nervous system (autonomic activation)
    - Respiratory system (in response to increased oxygen demand)

Increased sweating generates electrolyte imbalance leading to muscle cramps. Excessive vasodilation and water loss eventually leads to postural hypotension, low cerebral perfusion, and syncope (temporary loss of consciousness). Decreased cerebral blood flow may also be the initiating stimulus for increased blood–brain barrier permeability and brain injury.

Redirection of blood from central organs to the skin has been shown to stimulate oxidative/nitrosative stress and increase gastrointestinal ischemia and gut permeability. Gut permeability leads to a 'leaky gut' which enables leakage of endotoxins from the gut lumen into the systemic circulation, resulting in the activation of pro-inflammatory cytokines and other immune modulators.

Changes in gut epithelium such as reduced villus area are observed and may be a consequence of shifting of blood away from the gut to peripheral regions [18]. Increase in heart rate known as cardiovascular strain, can occur before a person's internal temperature starts to increase [19, 20].

Heat acclimatisation/acclimation: Humans can transiently adapt to heat exposure by optimising their ability to thermoregulate through a process known as heat acclimatisation, allowing them to better tolerate higher temperatures. This process is also referred to as heat acclimation.

- The term heat acclimation tends to be used in the context of 'artificial' environmental temperatures, for example purposeful heat exposure during a laboratory experiment or use of a sauna during an exercise heat tolerance training regime
- The term heat acclimatisation tends to be used to refer to natural environmental temperatures. In this report, we will use the term acclimatisation to encompass both

A person's level of acclimatisation plays an important role in how well they can tolerate hot and cold environments. When the environment around a person changes, for example when someone who lives in a temperate climate visits a tropical country, there will be a period during which the person becomes acclimatised to the new climate, both physiologically and behaviourally.

Heat acclimatisation can also be induced by purposeful repeated exposure to heat stress, with heat tolerance improving over time. This process can start in a few days and take up to six weeks or longer for maximum levels of heat tolerance to be reached, since some people are able to acclimatise quicker than others.

People who are well acclimatised to heat will sweat more, and their sweat is more diluted, meaning they lose fewer electrolytes through their sweat. They are considered to have a heat adapted phenotype. However, even a well acclimatised individual will ultimately have a temperature limit at which they are unable to thermoregulate effectively to maintain a stable core temperature.

In some regions, it is likely that the extreme temperatures that climate change is causing, and will cause in the coming decades, will exceed the human ability to thermoregulate.

Heat acclimatisation is a separate process from evolutionary adaptation to heat, which is when stable genetic changes occur over time, affecting core thermoregulatory mechanisms. It is possible that the ability to acclimatise could itself be an evolutionary adaptation. Heat adaptation is discussed further in Section 3.

Underlying conditions/heat-associated illnesses

Maintaining a steady body temperature puts a strain on the thermoregulatory system, which can lead to other health conditions such as cardiovascular events, kidney failure, epilepsy and gastrointestinal issues. In some circumstances an individual may be aware that they have an underlying condition that will be exacerbated by heat, but in other cases it may only become apparent once the individual is exposed to increased temperatures. This can include people who suffer from irritable bowel disease, a heart condition, epilepsy, or have kidney injury.

If the thermoregulation processes function as expected then the core body temperature would not be exceeded, but due to the pressure and strain on the body to maintain the body temperature a health crisis can take place when it is no longer able to regulate effectively. In some situations, the core temperature increases, resulting in heat illness.

Example: cardiovascular illness Extreme heat is associated with a greater risk of adverse cardiovascular events, especially for adults with pre-existing cardiovascular diseases [21].

Heatwaves have been demonstrated to increase the frequency of cardiovascular events such as heart failure and myocardial infarctions, which results in increased numbers of emergency department visits and hospitalisations [18].

The pathophysiology underlying the association between extreme heat and cardiovascular risk remains understudied. What is understood is that the blood vessels on the skin surface dilate during heat exposure in parallel to a redistribution of blood flow and volume towards the skin. Consequently, central blood volume is decreased and can be further reduced if fluid intake does not compensate for fluid lost through sweating.

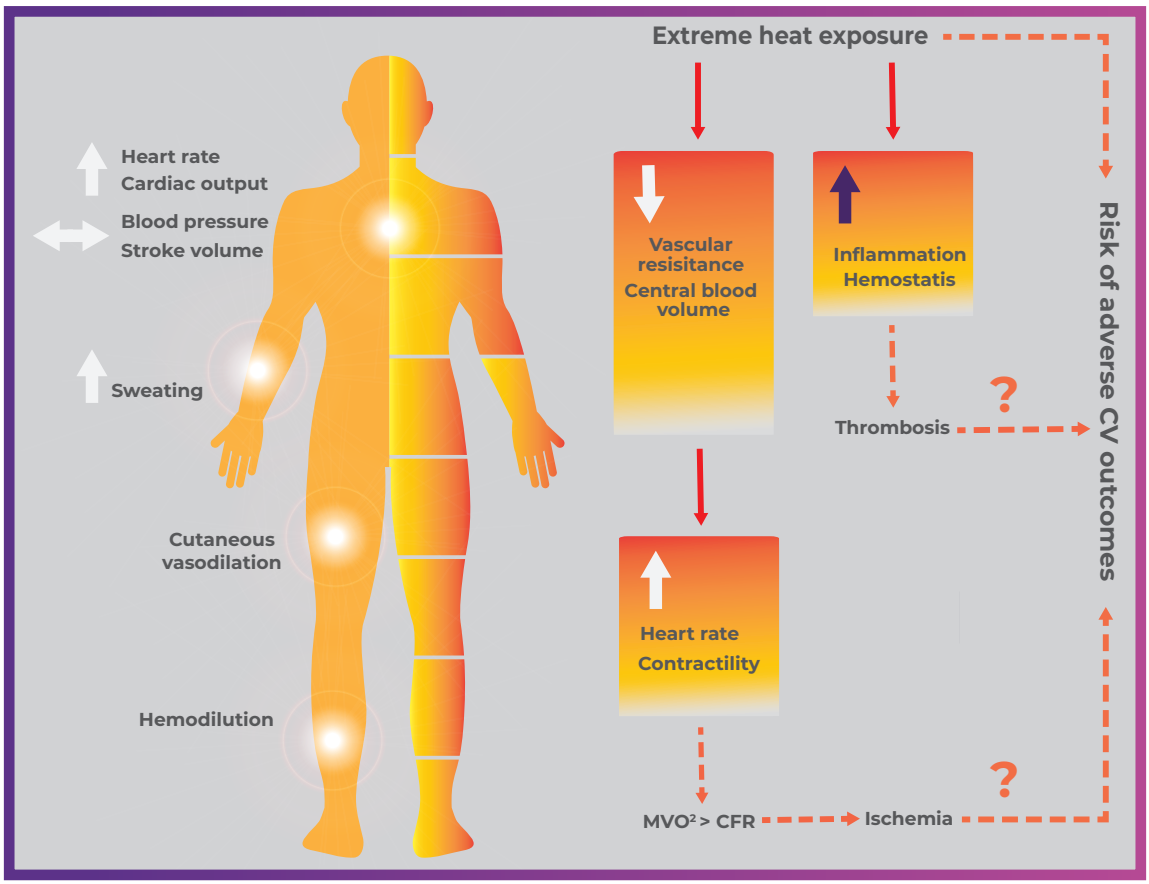
To counterbalance reduction in blood pressure, there is an increase in the heat rate, leading to greater need for oxygen. This may predispose some individuals to ischemic events. In addition, changes in blood fluidity due to dehydration may promote an environment that is prone to blood clots. Combined, these responses underlie the greater risk of adverse cardiovascular outcomes during extreme heat exposure (Figure 4) [21].

It has been demonstrated that young healthy individuals can experience cardiovascular strain, which is an increase in heart rate, with moderate temperature increases (up to 34°C) and before internal temperatures are affected [19].

According to a 2022 meta-analysis, a temperature increase of just 1°C is associated with a 2.1% increase in the risk of death related to cardiovascular disease and 0.5% increase in cardiovascular disease-related morbidity [22].

Figure 4. The potential pathophysiology mediating the relationship between extreme heat and adverse cardiovascular (CV) outcomes. (Figure adapted [21])

*MVO2 = Myocardial oxygen consumption, CFR = coronary flow rate



Heat Illnesses

Heat illness relates to serious medical conditions resulting from the body's inability to cope with a particular heat load. There are **classical (passively)** and **exertional (actively)** induced mechanisms of heat illness. Heat illnesses may be a protective mechanism that acts as a warning and inhibits activity during conditions of excessive heat stress. Their clinical presentation is a systemic illness with a broad range of symptoms and no single defining feature. The least severe form of heat illness is heat stress, followed by heat exhaustion, and then heatstroke, the most severe form which can lead to death. Early heat illness symptoms can be cramps, oedema - the swelling of ankles and feet, and heat rashes. (Table 1) [24].

Recovery from heat illnesses can impact on a person's quality of life as there can be lasting effects on their health if there is damage to the circulatory, renal, or neurological systems. This can also lead to increased susceptibility to other illnesses.

Heat stress describes the human body's inability to maintain a normal temperature. According to the American Conference of Governmental Industrial Hygienists (ACGIH) [23], heat stress is defined by the presence of any of the following conditions:

- Heart rate, in beats per minute (bpm), remains for several minutes above the calculated value of 180 bpm minus the individual's age (in years)
- Core body temperature is over 38.5°C for acclimatised individuals or over 38°C for unacclimatised individuals
- The recovery heart rate at one minute after peak physical effort exceeds 120 bpm
- Severe and sudden fatigue, nausea, vertigo or dizziness

The clinical presentation for **heat exhaustion** varies and includes a range of symptoms that present in cardiovascular, mental, neurological, renal, haematological and/or gastrointestinal systems (Table 1). Symptoms relate to the body's response to an excessive loss of water and salt, usually through excessive sweating. Heat exhaustion is related to high skin temperatures which are associated with changes in the pressure and volume of blood in the circulatory system resulting in cardiovascular strain, which is an increased heart rate [24]. There are early indications that cardiovascular strain occurs before body temperatures increase and could act as an early warning sign [19].

Heatstroke is life-threatening and the most severe form of heat-related illnesses. The transition from heat exhaustion to heatstroke is important to recognise and may occur quickly. It is characterised by the rapid rise of core body temperature from the optimal 37°C to above 40°C, and central nervous system dysfunction [25]. The natural course is quick, resulting in death in less than 24 hours if not recognised and treated.

The exact mechanism of heatstroke involving multiple organ dysfunction is not completely understood and its pathogenesis is complex. It involves inflammation, oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction. Brain and hepatic cells are sensitive to hyperthermia and irreversible neural damage begins at 40°C and progresses exponentially with temperature increases. Pathological studies on heatstroke patients reveal endothelial cell injury, inflammation, widespread thrombosis and bleeding in most organs.

Classic heatstroke results from passive exposure to extreme environmental heat. Physiological and morphological factors contribute to susceptibility to heatstroke. It often occurs as an epidemic during heat waves, particularly in the elderly, and contributes to 9-37% of heat-related fatalities during heatwaves [25].

Exertional heatstroke is characterised by an inability to thermoregulate during physical activity. Clinical features can include hyperthermia, nausea, abnormal heart rate, metabolic acidosis (chemical imbalances in the blood) and respiratory acidosis (increased carbon dioxide in the blood), muscle cramps, rhabdomyolysis (muscle injury resulting in release of proteins and electrolytes into the blood), elevated serum creatine kinase (enzyme that indicates muscle injury), cerebral dysfunction, seizures, multiorgan failure, disseminated intravascular coagulation (proteins that control blood clotting become overactive) and death. Rhabdomyolysis is a frequent manifestation

of exertional heatstroke but can also develop in the absence of an increased body temperature and is then termed exertional rhabdomyolysis. Exertional heatstroke affects predominantly young and healthy individuals and can cause sudden death in young athletes. It is an occupational hazard, particularly in the military.

Diagnosis of heatstroke is clinically based on neurological assessment, body temperature and history of heat exposure or exercise. The presence or absence of sweating is an unreliable guide to diagnosing or excluding heatstroke. Under intensive care, mortality reaches 26.5% and 63.2% in exertional and classic heatstroke, respectively [25].

The basic principle of heatstroke management is early resuscitation and immediate cooling. Cold water immersion or using fans to move air across the skin to enhance evaporation of sweat can be implemented based on specific patient characteristics such as age and overall health [26] and current environmental conditions.

Table 1: Symptoms seen in the clinical presentation of hyperthermia (increased body temperature) [24].

Body system	Heat exhaustion	Heatstroke (>40.5^{0}C core body temperature)
Mental state	Fatigue, thirst, irritability	Delirium, confusion, hallucinations, coma
Cutaneous	Sweating, flushed	Flushed, loss of sweating in classical, but not exertional, heatstroke
Cardiovascular	Rapid heart rate, drop in blood pressure	Heart failure, hypotension, myocardial injury
Muscular	Weakness, cramps	-
Neurological	Headache, dizziness, abnormal sensations (pins and needles)	Seizures / Epilepsy
Liver	-	Liver injury
Renal	Oliguria (low urine output)	Myoglobinuria (excess protein in urine), renal failure
Haematological	-	Blood clotting complications
Gastrointestinal	Nausea, vomiting	Mucosal swelling, vomiting

Cellular response to heat stress

Within just a few hours, heat may damage proteins, membrane lipids and nucleic acids, which are central to the structure and function of cells [25]. There is evidence of an inflammatory response being elicited in response to cell injury and cell death [25].

The severity of the cell injury depends on the level and duration of the increased body temperature starting at 38°C but particularly after 41.6°C when protein denaturation - the alteration and break down of the protein structure - will occur [27]. Increased misfolded and unfolded proteins results in cellular stress which causes the release of heat shock factors (HSF) and heat shock proteins (HSP). The heat stress response activates hundreds of genes related to the stress pathway and repair to microcellular damage [25].

Cellular damage alters a cell's electron balance, resulting in cellular dysfunction, tissue damage and death of the cell, potentially culminating in multiple organ damage and death. Injured cells undergo apoptosis (programmed cell death) or necrosis [25].

Because of cellular damage there is an upper limit temperature to which the body can respond, and extremely high core temperatures of over 49°C can give rise to cellular death from necrosis in less than five minutes.

Figure 5: Heat associated health risks. Maintaining a stable body temperature is vital for optimal biological function and the human body has adapted to maintain a stable core temperature to within a few degrees. To achieve this there are multisystem thermoregulatory processes in place. Left in figure: With increasing temperatures, different systems within the human body will be activated in response. Right in the figure: There are limits to the abilities of these systems and the impact of increasing temperatures can be different, depending on which systems is impacted or the most under strain

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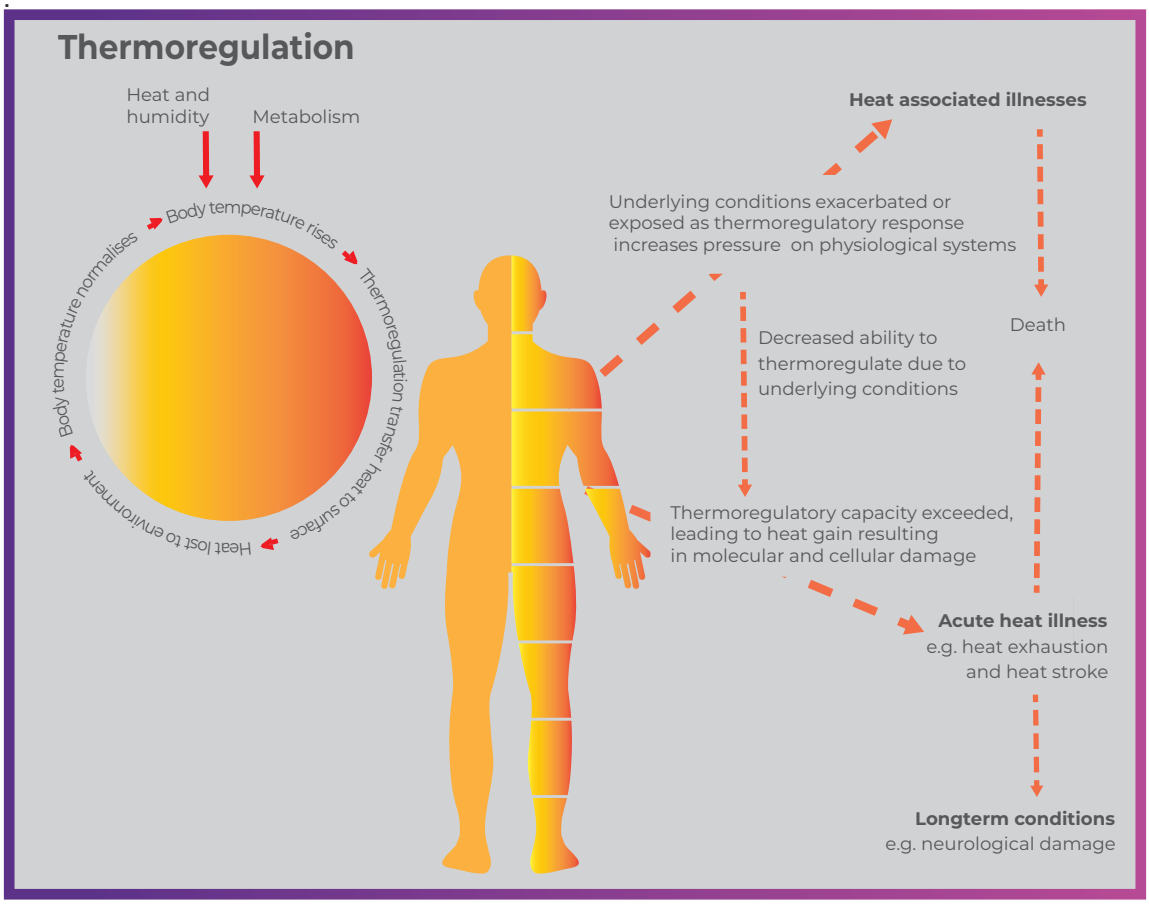

2.4 Who is at risk?

A population's risk from heat will vary depending on the level of exposure to high environmental temperatures, the amount of change in temperature and the responses to the heat exposure. However, for a given heat exposure event, different populations will also have different causes of heat related mortality and morbidity. This is partly due to the varying characteristics of the individuals who make up those populations, for example, demographics, occupations, and ability to avoid heat exposure.

There are populations at high-risk of heat illness. These are groups of people who do not have optimal thermoregulatory responses and include the elderly, young children, people with chronic conditions or people on certain medications, and pregnant women. In addition, certain jobs or activities require people to be subjected to hot and humid conditions, which may put their bodies at risk of heat-related illnesses and possibly result in death, for example military staff, construction or factory workers and emergency services. Between 2000 and 2016, the number of people exposed to heatwaves increased by around 125 million [9, 10].

UNICEF research found that 559 million children (24% of all children) are currently exposed to high heatwave frequency, and this is predicted to rise to 2.02 billion children (>99% of all children) globally by 2050. Furthermore, 624 million children are currently exposed to one of three other high heat measures – high heatwave duration, high heatwave severity or extreme high temperatures [11].

Factors related to avoiding/reducing heat exposure:

- Lifestyle and behaviour factors: e.g. ability to seek shade and air conditioning, reduce activity or exercise, drinking water, remove clothing, etc
- Infrastructure factors: availability of shade and clean water, air conditioning, heat reflective materials

Factors related to coping with heat exposure:

- Physiological factors: respiratory, cardiovascular and metabolic health, age, sex, pregnancy
- Acclimatisation: amount of previous heat exposure

There are many physiological factors that influence the ability to thermoregulate effectively and as a result the ability to tolerate increased temperatures. These range from stable factors such as biological sex and inherited conditions affecting components of the thermoregulatory system, to multiple modifiable factors such as fitness, body mass index and acclimatisation from previous heat exposure. The effectiveness of the thermoregulatory system is age-dependent, which is why there are higher mortality rates in infants and the elderly during heat extremes [25].

Avoiding exposure to heat is also recommended for outdoor sports activities with the national sports medicine authorities of the USA, Japan and Australia all recommending discretion when doing activities in wet blub temperatures over 28°C [12]. Low socioeconomic status has also been associated with increased risk of heat exposure and the associated morbidity and mortality [28, 29].

Heat related mortality and morbidity

Current data on heat related mortality has several limitations for understanding the health risks of heat exposure. Although mortality statistics during heat periods provide broad insights into which populations are most affected, they seldom reveal the specific causes of death.

For instance, it may be unclear whether the cause of death was a heat-related illness such as heatstroke or an underlying condition exacerbated by heat. In particular, for the latter category, medical records may not indicate that the cause of death was linked to heat, making direct associations difficult to confirm. Additionally, many individuals, especially in low to middle income countries, may not be able to access medical attention, resulting in undiagnosed heat related illnesses.

Due to the difficulty in documenting causes of death during heat extreme periods, excess deaths are often used as a proxy for the effects of heat in a population.

The effects of heat exposure on health may not be immediately evident. For example, a study conducted in London, UK showed that the excess risk of all-cause mortality from heat lasted for only two days and was followed by deficits in mortality that offset the excess mortality caused by heat by day 11, resulting in a net effect of zero [30]. This phenomenon was attributed to short term mortality displacement, where deaths that would have occurred anyway in frail individuals were brought forward a few days or weeks due to heat exposure. A study conducted in Delhi showed that the excess risk of mortality persisted for three weeks after heat exposure, followed by a mortality deficit that only partially offset the excess deaths [30]. These findings indicate that the excess risk of mortality from heat exposure can vary between regions.

Similarly, heat related morbidity is poorly documented compared to mortality, despite it having a major impact on health. For conditions exacerbated by heat, it may not be recorded that heat was a factor in the illness, especially if medical attention was only sought after the heat event had passed or a proper clinical assessment is done once the core body temperature is likely to have reduced.

Efforts are underway to better measure and classify those vulnerable to excess heat. The Lancet Countdown indicator for vulnerability to the extremes of heat is based on the following risk factors:

- Proportion of the population older than 65 years
- Prevalence of chronic respiratory disease, cardiovascular disease, and diabetes in the population
- Proportion of the total population living in urban areas.

These factors are combined with heatwave exposure data and the International Health Regulations capacity score, which is used to assess the level of 13 core capacities relevant to healthcare [6].

Based on this score for the 2021 report, since 1990, populations in very high human development index (HDI) countries have a 27-38% higher vulnerability than in low and medium HDI countries [12]. This is due to these regions having ageing populations, high prevalence of chronic disease, and rising levels of urbanisation.

In 2020 the European and Eastern Mediterranean regions were reported to be the most vulnerable of all the WHO regions to the extremes of heat. However, in the 2021 report vulnerability was shown to be increasing fastest in the low and medium HDI countries, increasing by 19% and 20% since 1990 in low and medium HDI countries respectively. The indicator will continue to be developed, for example it may incorporate specific heat adaptation measures such as the use of early warning systems and heat adaptation plans and urban greenness [6].

The results for the 2021 Lancet countdown report showed that global average heat-related mortality in over 65-year-olds reached a record high of 345,000 deaths, up ~16.6% from the 296,000 deaths in 2018 [12]. Between 2018 and 2019, all WHO regions, except Europe, saw an increase in heat related mortality, with India and Brazil seeing the biggest heat-related increase. Despite this the WHO European region still has the largest absolute levels of heat related mortality, at approximately 108,000 deaths in 2018. It is estimated that over 60,000 heat related deaths occurred in Europe between 30 May and 4 September 2022, the hottest European summer on record [13]. Work has already begun to develop this metric further to account for localised differences in response to heat exposure within and between countries, for example due to levels of urban green space and economic inequality [6].

2.5 Understanding the management of heat for health

In order to address the increasing health risks from heat to large sections of the global population, it will be necessary to refine current solutions to coping with heat and develop new ones:

- As weather patterns change, prevention programmes for extreme heat events should specifically target those most vulnerable to heat illness, thus reducing mortality. Effective targeting will be especially important in situations where resources for prevention are limited.
- Public health messages on effective strategies to remain cool are important. Understanding and developing effective strategies will require better knowledge of human physiological responses to heat in different sectors of the population and different settings. For example, the elderly typically have a poorer ability to sweat, so strategies that rely on sweat evaporation will be less appropriate for them. Current understanding of heat responses in different settings is limited.
- As a greater proportion of the global population is exposed to higher temperatures, better definition and recording of heat-related illnesses is needed. This should include events not solely due to overheating or during extreme heat events. Understanding the types and scale of the problem will help facilitate public health interventions, research and innovation in those areas where it can have the biggest impact on health.
- Development of better diagnostics and treatments as well as rehabilitation programmes would have valuable impact in identifying, managing and minimising the impact of heat illness.

Solutions are needed that do not exacerbate the underlying problem of climate change, i.e. they should preferably allow for mitigation as well as adaptation. For example, whilst air conditioning appears an obvious solution, current methods are often not sustainable and further contribute to the problem of global warming. Whereas tree planting is an example of an intervention that can provide shade, whilst also absorbing carbon dioxide.

There may also be a role for genomics in helping to meet some of these needs, for example to help identify who could be at highest risk of a heat related illness and to put targeted preventive measures in place.

The role of the genome

- Genetics and heat response
- Current state of the science
- How could genetic information be useful?

3.1 Genetics and heat response

The genetic basis of human responses to heat is not yet fully understood. As with most complex biological processes, it is likely these mechanisms are governed by activation and repression of specific genes. For example, the heat shock response is characterised by the increased expression of genes which accelerate the synthesis of protective heat shock proteins activated in response to cellular damage.

Genetic factors might contribute to various aspects of external heat tolerance and related health conditions, for example:

Thermoregulation

- Genes controlling heat sensing and thermoregulatory response mechanisms such as sweating and vasodilation
- Genes regulating baseline body temperatures e.g. the level of metabolic activity at rest or during exercise
- Genes regulating the general function of biological systems impacted by thermoregulation e.g. the cardio-respiratory and renal systems

Heat acclimatisation

- Genetic mechanisms related to temporarily improving thermoregulatory capacity due to previous heat exposure

Heat damage response

- Genes related to mechanisms for responses towards cellular and molecular damage that occurs during exposure to high core temperatures e.g. regulation of heat shock proteins

Is susceptibility to heat illness and heat-related illness heritable?

The concept that genetic variation can contribute to an individual's susceptibility or resistance to heat illness or heat-related illness is supported by instances of illness that cannot be fully explained by known lifestyle, environmental, or morphological factors. For example, when military personnel of similar age and fitness with no known health problems undergo the same level of exercise intensity in the same environmental conditions, a few may develop exertion-related heat illness while most do not. This suggests that genomic variation could affect an individual's risk of heat illness susceptibility or resistance by contributing to phenotypes that have not yet been identified. These phenotypes may be difficult to observe because they do not result in easily identifiable external morphological changes and/or only arise during a certain level of exertional heat exposure.

An alternative scenario involves individuals who suffer from heat-related illnesses and who have a known phenotypic risk factor that likely explains their susceptibility, for example a heart condition. Whilst for some individuals the underlying reasons for a phenotype may be largely due to environmental factors (e.g. a high-fat diet), others

may have specific genetic variants that put them at increased risk of developing the phenotype. Therefore, varying susceptibility could also result from the presence of genetic risk factors for phenotypes that are known to predispose an individual to heat-related illnesses.

It is possible that a combination of the two situations described above could arise, where those with the same known risk phenotypes for heat-related illness could still display differing susceptibility when exposed to the same environmental conditions. In this case these individuals may have genetic variants that make them more at-risk from a particular phenotype than others during exposure to heat.

For example, despite the presence of a heart condition some individuals may suffer heat-related illness and others may not, for reasons that cannot be fully explained. So genetic variation influencing susceptibility or resistance to heat illness will only impact the risk of people susceptible to heat-related illnesses.

Whilst all these hypotheses may be plausible, there is currently limited evidence to either support or refute them. The reasons for this and the types of evidence that could be used are below.

3.2 Current state of the science

Although the physiological basis of thermoregulation is understood, little information is available on the underlying genetic mechanisms. The molecular basis of a physiologically relevant heat damage response in humans is also relatively unknown.

This means that the role of genetic variation in individual human susceptibility to heat illness is not well understood. This lack of information is due to the limited research conducted on these topics and the complexities of studying heat response in humans, including genomic variation (Section 4).

Some studies have sought to understand the role of differing gene expression in thermoregulation and gain further insights into the general mechanisms of response to heat exposure. For example, transcriptional studies on changes in gene expression with increasing heat exposure are being used to identify genes important in thermoregulation via their activation in response to heat.

Another area of interest is understanding the role of epigenetic mechanisms in turning genes on and off during environmental exposures, including heat exposure. The field of environmental epigenetics is a new area of research and has mainly focused on non-human animals.

It has been observed that epigenetics plays a role in molecular adaptation to heat by producing a molecular ‘memory’ of past environmental exposures. The memory has been shown to decay over time, and to be reliant on the number of previous heat stress exposures endured. Moderate heat, over long periods of time, induces an 'adaptive' epigenetic memory, resulting in a condition of 'resilience' to future heat exposures. There is evidence that there are both adaptive and maladaptive epigenetic responses to heat that can be inherited, although current evidence is limited to organisms such as mice [31].

Research that has been done and can contribute to understanding the role of the genome and specific genes in heat response in humans can be broadly divided into three main areas:

- Species adaptation to extreme temperatures (evolutionary adaptation)
- Rare conditions linked to thermoregulation
- Exertional heat illness studies

Species' genetic adaptations to extreme temperatures

Multiple species of plants and animals have evolved genetic adaptations that allow them to tolerate high temperatures. Unlike humans, plants and animals can rarely modify their environments and must evolve adaptive physiological and behavioural mechanisms to cope with high environmental temperatures. For example, varying responses to heat stress have been reported between different breeds of livestock animals e.g. cattle, poultry and pigs [32].

Adaptation to heat tolerance has also been artificially introduced through genetic engineering of various thermoregulatory mechanisms. This has mostly taken place in plants, where the genetics of heat tolerance is much better understood and there has been a drive to develop heat tolerant crops [33].

There is also a drive to breed heat tolerant livestock, but difficulties in defining traits of heat resistance in animals and the complex thermoregulatory mechanisms involved means this research is less advanced, although the field is developing rapidly [34]. Despite this, cattle have been genetically modified for improved heat tolerance by altering one heat tolerance trait – the thickness of their coats [35]. This resulted in the first US Food and Drug Administration approval of gene edited beef for human consumption in March 2022.

While studies in animals and plants provide evidence to support the concept that key genes and genetic variants can regulate heat response, there are limitations to the extent to which this research can be applied to humans.

Animals have different thermoregulatory mechanisms to humans, for example many rely on panting rather than sweating. Additionally, animals that do sweat are often covered in fur, which changes the thermodynamic mechanisms of sweating. Lessons from animal research could be useful, but limitations will apply.

Studying the role of the genome in heat response is still complex in animals, but there are typically fewer variables to control for and fewer ethical challenges to consider. These types of research performed in animals may not be possible in humans.

Human populations are widely distributed across the globe, so it may be expected that different populations have also evolved differing responses to heat. Even when accounting for the ability of humans to readily change their environments, which is more achievable for cold than heat, a selection pressure for heat stress resistance remains [36]. Some underlying morphological traits that affect thermoregulatory ability appear

to differ between human populations. For example, populations indigenous to hotter regions typically have the largest surface area to body mass ratios [36].

For thermoregulatory mechanisms such as sweating or blood flow, according to a comprehensive review, there are no significant genetic differences between populations in the number of sweat glands, the sensitivity of glands to cholinergic stimulation, or in the core temperature threshold for the onset of sweating [37]. However, it is perhaps more likely that any differences that are seen between populations are due to both shorter and longer term acclimatisation of populations to their environment, with underlying thermoregulatory ability being a highly conserved trait among humans [36, 38].

On the other hand, it is possible that the ability to acclimatise to heat could itself be influenced by genetic variation, a topic which has been even less explored. Furthermore, research has taken place over several decades and often has limitations in terms of the design of the experiment not accounting for all the variables that integrate to control thermoregulation. For example, populations morphologically adapted to hotter climates due to their body mass to surface area ratio may not require additional sweating functions. Excess sweating may be a negative attribute if water is scarce and it has been observed that sweating is more conserved in indigenous people from hotter climates [36]. Research in this area would be useful, as improving our understanding of human evolutionary adaptation to environmental temperatures could help identify key thermoregulatory genes and their mechanistic pathways.

Rare conditions related to thermoregulation

There are several rare genetic conditions where individuals have features of a dysfunctional thermoregulatory response. This includes symptoms of overheating such as feeling hot, high heart rate and sweating, even at relatively low levels of heat exposure. There is research exploring whether genetic variation causes abnormal levels of heat intolerance.

Whilst these conditions are rare and do not always result in typical symptoms of heat related illness, they can help identify the broader genetic mechanisms underlying thermoregulation and heat response in humans.

Example: Anhidrosis (reduced sweat production)

Ectodermal dysplasias are a group of disorders which typically affect the hair, teeth, nails, sweat glands, and/or skin. Hypohidrotic ectodermal dysplasia (HED) is a rare condition which causes anhidrosis, where despite morphologically normal sweat glands patients have reduced or absent sweat production in response to stimuli such as external heat or exercise. This increases the risk of hyperthermia and heatstroke during exposure to high temperatures.

A causative loss-of-function mutation has been identified in a single gene (*ITPR2*) which prevents promotion of the release of calcium necessary for normal sweat production [39]. Other patients with mutations causing different ectodermal dysplasia's which affect the activation or functioning of sweat glands are at higher risk of heat illnesses from heat exposure [40].

Congenital insensitivity to pain with anhidrosis (CIPA) is another very rare autosomal recessive genetic disorder where patients suffer from anhidrosis. However, patients are also insensitive to pain and temperature, so in addition to being unable to sweat, they also cannot sense heat to take action to avoid it. They are at risk of hyperthermia even at ambient temperatures, so are at particular risk from excess heat exposure. The condition is caused by mutations in the *NTRK1* gene which results in downstream loss of nerve growth factor-dependent neurons in the peripheral nervous system, causing the symptoms [41].

Example: Cystic Fibrosis

Cystic Fibrosis is an autosomal recessive disorder predominantly found in European populations, where it occurs in approximately 1 in 3,000 live births. The disease is caused by a mutation in the gene that encodes the cystic fibrosis transmembrane conductance regulator (*CFTR*) chlorine ion channel, which is involved in salt and water transport across cell membranes. A key symptom of the disease is abnormally salty sweat, and that patients are particularly at risk for heat illness during high environmental temperatures [42]. It is thought this is because the excessive amount of salt lost through sweating causes low levels of sodium in the blood and a corresponding low vascular volume, leading to circulatory collapse and hyperthermia [42].

Example: Neuropathies

Erythromelalgia is a rare neuropathy that mostly affects the extremities, usually the feet but sometimes the hands [43]. The main symptoms are warmth, redness and burning pain, especially in the affected extremities. Heat is a trigger, as well as exercise and standing. Therefore, prevention strategies include staying in cool locations and avoiding high temperatures, whilst relief from symptoms can be achieved via cool water immersion or use of fans.

Primary erythromelalgia arises in isolation from other conditions and can be idiopathic (without known cause) or inherited. The incidence of primary erythromelalgia ranges from 0.36 to 1.1 per 100,000 people [44]. The inherited form is associated with mutations in the gene *SCN9A*, which encodes a voltage-gated sodium channel.

Secondary erythromelalgia arises due to other underlying conditions, most commonly myeloproliferative disorders such as polycythaemia vera and essential thrombocytosis, where the body makes too many blood cells. Whilst cooling is important in preventing and managing both primary and secondary erythromelalgia, other treatments are more specific to the underlying cause of the disease. For example, aspirin is a key treatment for secondary erythromelalgia caused by myeloproliferative disorders, but is less effective in primary erythromelalgia, where medications affecting the voltage-gated sodium channels are more promising [43].

Other conditions include hereditary sensory and autonomic neuropathies [45] which are characterised by progressive loss of function that predominantly affects the peripheral sensory nerves. A variety of symptoms occur that include sweating issues, inability to sense heat or cold, or having sensations of heat unrelated to the temperature of the external environment. Their incidence has been estimated to be about 1 in 250,000.

Example: peripheral innocuous warmth sensitivity

The perception of innocuous warmth – temperatures around 1.3 to 6.2°C above baseline skin temperature – is triggered by activation of a subpopulation of peripheral thermosensory neurons. There is also growing evidence that thermotransduction by nonneuronal cells, such as skin keratinocytes, might contribute to or modulate a person's perception of thermal stimuli.

While the precise molecular mechanisms underlying warmth transduction are still being revealed, recent genetics studies have provided evidence for the *TRPV1* and *TRPM2* genes in mammals. These are members of the transient receptor potential (TRP) ion channel family, transducing molecules that appear to confer thermosensitivity upon the sensory neurons that detect warmth, and/or neighbouring cell types [46, 47].

There is some evidence in mice that deletion of *TRPM2* affects warmth perception, but evidence in humans in lacking. However these genes could be candidates for study in terms of understanding the physiology of human heat response, and whether variants in these genes impact human health due to maladaptive warmth perception.

Exertional heat illness

Exertional heat illness is characterised by an inability to thermoregulate during physical activity, which can result in heatstroke and sudden death even in young and fit athletes. Whilst excess internal heat generated via exercise related metabolic activity is the primary cause, environmental heat exposure puts additional stress on the thermoregulatory system. Therefore, high temperatures increase the chance of exertional heat illness, and at sufficiently high temperatures anyone could develop exertional heat illness.

Exertional heat illness is an area where the role of genetic variation underlying susceptibility to heat has been explored in normal, healthy individuals who have been exposed to potentially hazardous temperatures, often due to their occupations in the military, as rescue workers, as construction/industrial/agricultural labourers, as athletes, or as amateur sports participants.

For example, under the same environmental conditions, some fit individuals experience severe exercise related heatstroke and/or death, whilst others remain unaffected [48]. It is an area of active interest to conduct research in order to optimise performance, e.g. of military or emergency personnel and athletes in warm environments.

Parallels have been drawn between cases of exertional heatstroke, exertional rhabdomyolysis and the condition malignant hyperthermia (MH) due to the similar symptoms experienced [49]. MH is a potentially fatal condition where patients have a severe reaction to some drugs used in anaesthetics, which results in hyperthermia alongside other symptoms, including rhabdomyolysis. Around 75% of cases are caused by variants in the skeletal muscle-specific calcium channel gene *RYR1*, although it can also be caused by variants in other genes involved in calcium regulation such as *CACNA1S*.

In patients with these variants, calcium releasing agents including anaesthetics trigger an uncontrolled release of calcium into the muscle cells, leading to elevated metabolism and hyperthermia. *RYR1* has also been identified in the heritability of exertional heat illness [48, 50]. However it has been suggested that other defects, or combinations of defects, in skeletal muscle calcium homeostasis, oxidative metabolism and membrane excitability are associated with exertional heat illness [48].

More genetic variants which appear linked to both exertional heatstroke and MH susceptibility have recently been discovered, for example in a protein called *ASPH* gene encoding junction, which also regulates calcium dynamics in muscle cells [51]. Despite this evidence of a genetic basis to exertional heat illness, its similarity to MH is still unclear, and their molecular mechanisms require further exploration.

Whilst some mechanisms may be specific to exertion related heat illness, it is likely that there is overlap with general thermoregulation, meaning lessons from this field could also be applied to non-exertion related heat illness. However, research is needed in the relevant populations.

3.3 How could genetic information be useful?

If the role of the genome and/or key genetic variants is better understood, there are several ways in which this could benefit the prevention and management of heat related illnesses.

- New diagnostics

Genomic research results could improve our understanding of the molecular mechanisms underlying heat illnesses and heat-related illnesses. There are currently no diagnostics specific to heat illness. Further research would be valuable to investigate whether better biomarkers can be identified in order to diagnose heat illnesses more accurately. Tests could also facilitate rehabilitation by monitoring progress in recovery from a heat illness.

- Better treatments

In addition, treatment of heat illness is quite rudimentary, based on cooling. Whilst this is effective, a better understanding of the molecular basis of heat illness could lead to more specific treatments for the various symptoms that arise. This could potentially help prevent or better treat the longer-term complications of heat illness, for example damage to neurological function. This is especially the case for those people unable to access rapid cooling in time, by helping prevent or treat heat damage. If the general mechanisms that control heat response are better understood there may also be prophylactic therapies that could be developed to enable people to cope with ever-warming climates.

- Identify people most susceptible to heat illness

If certain genetic variants are found to be associated with increased risk of heat illness or heat-related illness, this could be used to help identify individuals most susceptible to heat related conditions. These individuals could then be advised to take precautions during extreme heat events.

A risk assessment could be used to help prioritise people who may need access to interventions to reduce heat exposure to allow them to better manage heat exposure. For example, as there is a need to mitigate climate change by reducing energy usage, energy intensive interventions such as air conditioning could be prioritised for those at highest risk, including genetic risk. Alternatively medications to improve heat response (e.g. to increase sweating) could be prescribed.

The information could also be used to help assess whether individuals are suitable for particular occupations or activities involving exposure to extreme temperatures. This may be identifying those who have more robust heat acclimatisation responses. The utility of heat illness risk prediction is being explored for both work and leisure related activities, but does not currently include genetic information [52].

- **Identify people susceptible to severe outcomes from heat illness**

As well as identifying individuals most susceptible to heat illness, understanding of genetic factors could likewise help to identify individuals who are likely to suffer the most severe outcomes when affected by heat illness. This would allow better prioritisation of prevention, diagnosis and intensive care.

- **Develop more targeted and personalised therapies**

There are a variety of mechanisms that can affect heat response in individuals based on their genomic profile. Understanding the precise mechanisms underlying an individual's genetic risk could enable more targeted and effective treatment – assuming a variety of treatments are available. For example, one treatment for heat response may work by reducing metabolic heat, whilst another may work by regulating sweating. By understanding whether the cause of an individual's underlying heat susceptibility is due to a variant mediating metabolism or perspiration or cardiovascular strain, that person could be matched to the most appropriate treatment for them, whilst potentially avoiding unwanted side effects from incorrect treatment.

- **Reduce thermoregulatory side effects of medicines**

Understanding which medications could affect heat response may provide indicators for which medications may produce adverse side effects in warmer climates. Commonly used medications for chronic conditions, e.g. diuretics and antipsychotics disrupt thermoregulation or fluid/electrolyte balance and may sensitise patients to heat. Pharmacogenomic information for these medications could determine whether dosage adjustments are needed and whether medications could be avoided in certain climates or be used to develop advice that they should not be taken when the patient is in hot conditions.

Challenges of studying human response to heat exposure

- Challenges for research
- Genetic research needs and challenges

4.1 Challenges for research

Research into the human body's complex response to increasing temperatures needs to include the factors that influence a person's heat response, for example their heat susceptibility, health, adaptive behaviour, and environmental situation including the built environment. The challenges around studying human response to heat exposure include:

- **Multiple factors contributing to the response to heat**

The multiple contributions of different physiological and environmental factors that modulate an individual's overall response to heat exposure can make identifying contributing factors difficult. This is a challenge experienced in other areas of research, such as nutritional research or investigating determinants of respiratory health from air pollution exposure, and lessons on how to do this research could be learned from these areas.

Most heat response research requires multiple parameters to be measured and controlled therefore is more likely to be done in small highly defined cohorts. With the increased availability of digital technologies, wearable devices and computational power it may in the future become easier to capture, analyse and interpret the complex interplay between the changing environment and the human response.

- **Quantification of heat exposure**

Unlike with plants and many animals, the temperature of the climate is not the same as the temperature a human population is exposed to, as humans are often able to modify their environment via changing the room temperature, or even changing their clothing. Therefore environmental temperature records to monitor a person's exposure may not be useful. As well as maximum temperature of heat exposure, it is important to consider its duration. The level of prior heat exposure that has enabled individuals to acclimatise is also difficult to quantify, but can contribute to their ability to cope with increased temperatures.

Advances in non-invasive, easy to use and continuous monitoring devices will improve the ability to monitor physiological features related to heat exposure. The new technologies includes digital pills to monitor core body temperatures, wearables for monitoring changes in sweat electrolyte concentrations and continuous heart rate monitoring. The use of multiple types of data to develop multivariable models for risk prediction are worth exploring.

- **Measures of core body temperature**

There is not a standardised method to measure characteristics important to understanding heat response, such as heat stress and core body temperature. The recommended measure of core body temperature is rectal temperature. This may not be possible when a potential heat stroke victim experiences symptoms and is more likely to have their core body temperature checked when in hospital and may already be recovering from extreme high core temperatures. Therefore the true core body temperature that could be causing illness is often unknown.

◆ External versus internal heat generation

Internal heat sources, from metabolic processes (such as exercise) or inflammatory responses (fever), lead to systemic responses that can overlap with thermoregulatory responses to external heat. The result is that these processes result in a complex interaction.

For example, some features (such as heat shock proteins) have extensive roles in these responses. Therefore, when investigating these mechanisms that have the potential to be activated by different types of heat, it is important to be able to determine the original source of the heat.

◆ Determining what disease is being investigated

Heat is an environmental exposure and the response mechanisms to heat are systemic and complex. A variety and range of responses can take place that rely on a number of systems and organs that may have other underlying morbidities that exacerbate the effects due to the heat response.

Phenotypes may not be easily identifiable, and/or may only arise during a certain level of heat exposure. Therefore, there is no single disease phenotype or definition for 'heat illness' identified, making it more complex to carry out research **in** a defined cohort. Rather a common series of symptoms and the context (i.e. heat exposure from hot weather) have been used to extrapolate that heat illness is the likely cause of symptoms being experienced in patients.

That a series of symptoms are present also points towards a syndrome, i.e. a set of medical signs and symptoms which are correlated with each other and often associated with a particular disease or disorder.

Identifying features for heat susceptibility or resistance can be challenging because these traits may not result in easily identifiable external morphological changes. Researchers could study populations living in different climates or that experience extreme temperature changes to identify traits that may confer heat susceptibility or resistance.

◆ No biomarkers for heatstroke

No adequate biomarkers - genetic or non-genetic - for the identification of heat stress or heatstroke have been identified. Biomarkers currently in use are related to cellular damage. This can also make it more difficult to confirm heat as a cause of illness once core body temperatures are normal again.

◆ Absolute versus relative temperature changes (fluctuation and duration)

With changing climates there will be increased human exposure to increasing average temperatures, as well as heatwaves. Each of these will have different mechanisms for response and adaptation. In the short term, heatwaves will have the most adverse effects on human health, and their impact will depend on the level of the temperature fluctuation from average as well as their duration.

4.2 Genetic research needs and challenges

Capturing which environmental variables are influencing health is complex, as is determining what proportion of the response is attributable to genetics and the environment.

This is an issue that is not new to the field of genomics research. For example, host genomics studies consider the exposure to infections, and nutrigenomics studies consider which nutrients are being consumed.

Understanding the complex environmental and genetic factors that contribute to different health conditions is not a new research concept, and sharing expertise on how to do this type of research across different fields could be valuable.

What is new is the consideration of environmental heat exposure and how human responses to this exposure is influenced by genetic factors. Evidence is currently very limited on which genetic variants are responsible for differing susceptibility to heat exposure and for regulating human physiological responses, particularly in real world / non laboratory settings.

Therefore, further research is needed specifically on which specific genes and genetic variants can control heat response. This could be achieved by projects investigating human heat response including genomics research in their programmes.

Alternatively, if it is possible to capture an individual's heat response (such as through wearables, blood tests, chamber experiments or questionnaires), then heat response research could be incorporated into larger population wide research projects, especially those, such as UK Biobank, which have a genomics component. There is potential for combining data from existing longitudinal population studies with climate data [53].

Next steps for research

- Next steps for research

5.1 Next steps for research

Peoples' abilities to respond to heat will become more relevant as global temperatures rise. This provides a reason to plan and execute research strategies to improve our understanding of this growing health threat.

The role that genomics has in heat response is unclear. There remains a need for basic research and increased understanding of the physiological responses to heat exposure as well as research on epigenetics and gene-environmental heat interactions. These could enhance individual risk prediction to heat stress as well as provide targeted prevention and better protection of population health.

There is also a need to develop specific diagnostic tests and therapies for early recognition for heat illnesses, in particular heatstroke, and to identify those as risk of death or developing life altering complications as a result [25].

Thermoregulatory responses are a systemic response to changing temperatures and exertional heat illness research and the genetics of rare diseases indicate a genetic component. As research into heat response and human health progresses, it is likely that the role of the genome will become clearer.

There is research activity in the areas of heat response, health risks and rare conditions that have an element of a thermal dysregulation. However, the work is fragmented across and between disciplines. It is not being done from the perspective of climate change or global warming. There is therefore good reason to provide support for focused and coordinated efforts for research on the health impacts of climate change.

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