Chapter 6
Heat Waves and Rising Temperatures: Human Health Impacts and the Determinants of Vulnerability

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Abstract Globally, heat waves account for dramatic increases in mortality and morbidity; however, there is increasing awareness that day-to-day increases in temperature contribute to a significant risk of heat-related morbidity and mortality (HRMM) that over one or more warm seasons may exceed the public health burden of heat waves. Climate change has already and will continue to increase both average ambient temperatures and the frequency and intensity of excursions above those averages (i.e., heat waves or extreme heat events) and will thereby lead directly and indirectly to amplification of the risk of HRMM. This chapter provides a brief synopsis of our current knowledge about thermoregulation, thermotolerance and the pathophysiology of heat stroke, and the multiple determinants of health and illness that influence the risk of HRMM and that collectively define vulnerability. A particular focus is on two vulnerable populations, older adults and children. An Environmental Health Multiple-Determinant Model of Vulnerability is presented as a conceptual framework to integrate that knowledge, with the intent of providing a tool that can facilitate compilation and translation of the information to interventions and adaptation strategies relevant at the individual level and/or subpopulation and population levels and at one or more geopolitical scales in developing and/or developed nations. Three overarching strategies for HRMM risk reduction are discussed, including Extreme Heat Event and Warm Season Heat Preparedness and Response Action Plans, Promote Good Health and Access to Quality Healthcare (reduces risk and increases resiliency), and Reduce/Manage Potential Exposure(s) (individual, community) to Ambient Heat and Other Physical Environmental Stressors. A key focus of this chapter is on integration and translation of knowledge.

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Over evolutionary time scales, humans have evolved to tolerate ambient heat across a fairly wide range of environmental conditions; that ability is enabled by behavioral and complex biological/physiological thermoregulatory adaptations that serve to maintain an average core body temperature within a narrow life-sustaining range around 37 °C (98.6 °F) [1] regardless where they live or where their ancestors evolved [2]. Under past and present climatic conditions, human populations around the globe have been and continue to be exposed to periods of *extreme* high temperatures that pose a risk of adverse health impacts, which include but are not limited to a suite of mild-to-severe conditions within the rubric of "heat-related illness (HRI)," and acute exacerbations of prevalent chronic diseases [3, 4], as well as death that may or may not be attributed as a direct or indirect consequence of heat exposure or a combination of heat and comorbidity. Climate change has already and will continue to increase both average ambient temperatures and the frequency and intensity of excursions above those averages [5] and will thereby lead directly and indirectly to amplification of the risk of heat-related morbidity and mortality (HRMM) [6]. (Key terms used in this chapter are defined in Table 6.1).

Modern societies, especially politically and economically stable nations, have social systems that include mechanisms designed to protect the stability of the society by reducing the health risks and/or increase the resilience of the overall population during natural disasters, including heat waves or more generally "extreme heat events" (EHE) (see Table 6.1). Thus one would expect, at least in developed nations, for there to be sufficient experience and knowledge, guidance, policies, and infrastructure to adequately protect the population's health during EHE. This expectation was proven wrong in 2003, when an intense and extended heat wave and exceptionally hot summer in Europe claimed about 70,000 lives [7])—with about 15,000 deaths occurring in France alone [8]. Extreme heat exposure remains the leading cause of weather-related deaths in the United States [9]. Although the death toll paled in comparison to the 2003 European heat wave, the summer 2006 California heat wave, which affected most of the State and was of unprecedented intensity (with both extreme high daytime maximum temperatures and high nighttime minimum temperatures) and duration (about 17 days) [10, 11], had a very significant public health burden. That event is estimated to have resulted in over 600 excess deaths [12, 13] and about 1,200 excess hospitalizations and 16,000 excess emergency department contacts for a variety of causes [14]. The economic cost of the health impacts (mortality and morbidity) of that event has been estimated to have been $5.4 billion [15].

Importantly, although less dramatic than a heat wave-related sudden upsurge in deaths and illnesses, there are significant health risks associated with day-to-day excursions in temperature above local warm season means that might not meet a

Table 6.1 Glossary of terms

Heat-related morbidity and mortality (HRMM): this term is used here to reflect the full-spectrum of causes of illness or death, including heat-related illness (HRI; a clinically defined spectrum of conditions associated with excessive heat stress). The abbreviation HRI is used when explicitly referring to one or more conditions within the spectrum of heat-related illnesses
Heat wave (extreme heat event): there is no universally accepted definition of "heat wave"; however, commonly applied criteria include the occurrence of temperatures, or a temperature plus humidity metric (e.g., Heat Index or Humidex) above a threshold level that persists over 2 or 3 consecutive days. The term extreme (or excessive) heat event (EHE) is generally used synonymously with "heat wave"; for the purposes of this chapter, the term is used to represent any extreme excursion above usual average temperature conditions that may pose a health risk, regardless of whether it meets criteria for designation as a heat wave
Vulnerability: the definition applied in this chapter (see text) has a public health orientation and differs from the definition used by the IPCC (Climate Change 2007: Synthesis Report), which states: *Vulnerability is the degree to which a system is susceptible to, and unable to cope with, adverse effects of climate change, including climate variability and extremes. Vulnerability is a function of the character, magnitude, and rate of climate change and variation to which a system is exposed, its sensitivity, and its adaptive capacity*
Heat stress: *heat stress* is defined as the total heat load on the body from metabolic heat production plus external environmental factors; and *Heat Strain* is the total physiological stresses resulting from heat stress. An alternate common *heat stress* definition combines heat load and its consequences: *Heat Stress is any combination of work, airflow, humidity, air temperature, thermal radiation, or internal body condition that strains the body as it tries to regulate its temperature. When the strain to regulate body temperature exceeds the body's capability to adjust, heat stress has become excessive* (US Navy definition)
Heat acclimatization: the terms *heat acclimatization* and *heat acclimation* are often used interchangeably; however, acclimatization refers to adaptations that develop as a result of challenges in the natural environment (e.g., physical training in a hot country), and acclimation refers to similar adaptations acquired from experimental exposure to artificial conditions
Climate change mitigation strategies (CCMS): actions to limit further climate change by reducing the production of greenhouse gases (GHG)
Climate change adaptation strategies (CCAS): actions to lessen the adverse impacts by preparing for inevitable changes in climate and climate variability

definition of "extreme" heat and that might not be perceived by the overall population and specific at-risk subpopulations as hazardous [16–21]. In a meta-regression analysis using published results from multiple cities around the world, it was estimated that in nearly half of those locations, the risk of all-cause (all-age) mortality increased by one to three percent (1–3 %) per 1 °C increase above the city-specific threshold (i.e., the temperature at which the mortality/morbidity indicator is lowest or the temperature where there is a sharp increase in a nonlinear exposure-response function) with the effect estimate (i.e., slope of linear-response function) varying by different city-specific characteristics and a general trend for the thresholds to be higher in locations closer to the equator [17]. Geographic patterns in effects have been reported in a number of studies, for example, heat-related mortality in the United States tends to be greater in communities in cooler climates than in warmer climates; the smaller effect in warmer areas has been attributed to adaptation through physiological, behavioral, technological means [22–27].

A few studies have evaluated the added heat wave effect above the overall warm season increase in mortality. For example, in a meta-analysis of seven California counties, the July 2006 heat wave was associated with a 9 % (95 % CI: 1.6, 16.3) increase in all-cause daily mortality per 10 °F (5.6 °C approximately) change in apparent temperature or about threefold the effect estimated over the entire warm season (May–September) or July only in 1999–2005 [13]. That magnitude of added heat wave effect is consistent with those observed for some European cities [16]. Over one or multiple warm seasons and over large geographic areas with exposed populations, the increased risks associated with non-extreme temperatures, reflected in increases in numbers of deaths and emergency department visits or hospitalizations, are a major contributor to the cumulative public health and healthcare burden of ambient heat, potentially greater than heat wave periods (which are relatively rare) [16, 17, 28].

Organizations charged with protecting public health during natural disasters are becoming more aware of the potential for health effects (mortality or morbidity) to occur not only during EHE but also at less-than-extreme temperatures common over a warm season. However, most if not all of those organizations continue to use extreme heat alert systems and HRMM risk-reduction strategies that are formulated from an "emergency response" perspective and involve implementation of public health protection protocols that are triggered by forecasted or observed temperatures (or other biometeorological measures) that meet criteria for "extreme" heat conditions. Furthermore, to date, those criteria are always based on exposure-response functions derived from mortality studies, in part because there are overall and for specific locations far fewer studies of ambient heat impacts on morbidity than on mortality. Given that even under current climatologic conditions, ambient heat continues to lead to significant morbidity and mortality, despite the fact that HRI is potentially preventable [3, 9, 29] as is most of the excess HRMM observed in epidemiologic studies makes it clear that improved approaches for prevention of HRMM need to be developed and implemented in the near term. It will be essential to augment the emergency response approach and add a broad suite of strategies that aim to diminish individual and population risk under the full range of ambient heat conditions, not just extremes. To that end, it is necessary to identify the populations, subpopulations, and individuals at elevated risk and to define and understand the independent and joint influence of determinants that contribute to greater (or diminished) *vulnerability* (see Table 6.1 and next section). Furthermore, while epidemiologic observations and research conducted at the population level is critically important and has been invaluable in guiding current strategies for reducing HRMM, the existent burden of HRMM and the amplified challenges to public health posed by climate change and other global changes, such as migration to urban areas or increased prevalence of chronic diseases, that are adversely affecting population health and resilience make it essential that the science upon which risk-reduction strategies are based is broadened. Major advances in our understanding of the pathophysiology of HRI and how it may be related to underlying heath status, in particular the role of the immune system (innate and adaptive) and systemic inflammation and oxidative stress [1, 3, 30–32], can provide critical insights to which

individuals and populations are most susceptible to HRMM and can guide identification of efficacious and cost-effective interventions.

This chapter provides a brief synopsis of our current knowledge about the multiple determinants of health and illness that influence the risk of HRMM and that collectively define vulnerability. A conceptual framework to integrate that knowledge is presented, with the intent of providing a tool that can facilitate compilation and translation of the information to interventions and adaptation strategies relevant at the individual level and/or subpopulation and population levels and at one or more geopolitical scales in developing and/or developed nations. The scope of this chapter does not allow a comprehensive exposition of the determinants of risk for all vulnerable populations; however, recent advances in knowledge about thermoregulation and risk factors in older adults and children are briefly discussed. Strategies for HRMM prevention are identified.

Vulnerable Populations: Multiple Determinants of Ambient Heat Health Impacts

Populations and Subgroups at Elevated Risk: Insights from Epidemiology

Identification of vulnerable populations for the purposes of developing public health approaches to prevention of HRI and HRMM is primarily based on epidemiologic studies that utilize routinely collected administrative data (death certificates, hospital admissions, and emergency department contacts). A number of mortality and morbidity studies (case-control, case cross-over, time-series, and case-series) have evaluated the impacts of ambient heat on specific subpopulations defined by diagnosis group (i.e., to identify cases for specific-cause analyses), age, sex, race/ethnicity, or activity if the data are available (e.g., occupational workers, athletes) and/or evaluated the influence of population-specific or location-specific factors, such as socioeconomic indicators or co-exposure to air pollution either as potential confounders or as effect modifiers. Direct comparison of individual epidemiologic study results is challenging due to differences in study populations, locations, and designs, in particular the use of different temperature indicators and/or different definitions of a heat wave, and whether potential confounding or modifying factors have been considered [18, 33]. Importantly, the commonly used epidemiologic data and study designs preclude detailed examination of individual-level factors, such as obesity or comorbidity and treatment, or location-time-activity patterns that can modify exposures and that may account for the enhanced risk observed at the population level; thus, clear attribution of the elevated risk to just biological susceptibility or another factor is not possible. (For recent reviews of the epidemiologic literature on temperature effects on all-cause or specific causes of mortality, see Hajat and colleagues (2010) [17] or morbidity see Ye and colleagues (2012) [18]. In addition, see Smith and colleagues (2012) for a discussion of heat wave definitions [33]).

Among the different studies, there is heterogeneity in the results for some key factors, i.e., whether there is an effect or association and the direction and magnitude of the association, with some of the differences likely a function of whether the study is examining mortality or morbidity and the specific diagnoses being examined [17, 18, 34]. Age, specifically older adults (usually defined as ≥60 years of age) and the very young (infants, children <5 years of age), is among the strongest and most consistent predictors of elevated risk for HRMM [14, 17, 18, 34]. There are mixed results for sex, with some studies indicating no influence, and others suggesting women or men are at greater risk (often dependent on the health outcome) [17, 18, 34]. Predisposing chronic diseases (e.g., psychiatric illness and neurological disorders, cardiovascular and pulmonary diseases, and diabetes) are also consistently implicated in elevated risk for HRMM [17, 18, 34, 35]. Other factors prognostic of increased risk of HRMM include: being confined to bed, not leaving home daily, and being unable to care for oneself [36]; various general indicators of being socially isolated (e.g., living alone, presence of or frequency of social contacts, or linguistically isolated) [36–40]; and persons who are socioeconomically disadvantaged [36–40]. Interestingly, some studies have indicated the higher risk associated with socioeconomic factors exists for American but not European cities [41], although in France during the 2003 heat wave, for older adults income was associated with greater risk of mortality [42]. Dehydration in general and dehydration associated with medications (neurological and non-neurological) that impair thermoregulation or thirst regulation were also significantly associated with elevated risk of mortality during the 2003 heat wave in France [43]. Factors associated with lower risk include air conditioning (as indicated by air conditioning saturation in a community or evidence of functional/used home air conditioning), visiting cool environments, and increasing social contacts [36, 44].

Environmental Health Multiple-Determinant Model of Vulnerability

Multiple (or Multi-) Determinant Models (MDM) are increasingly being used (qualitatively and quantitatively) to evaluate complex multifactorial chronic disease processes and incorporate consideration of a broad range of risk factors, especially host factors and social determinants of health. This approach is consistent with a paradigm shift by major public health organizations (e.g., WHO, US NIH, and CDC) from a model that just focuses on the determinants of health and disease at the individual level to a holistic model that considers the individual and populations within the context of their physical, societal/cultural, and economic environments across the lifespan [45, 46]. As is the case for complex diseases, complex environmental problems require a holistic approach. Figure 6.1 presents a schematic of the *Environmental Health Multiple-Determinant Model of Vulnerability* (*MDMv*), which is proposed here as a conceptual framework to evaluate the global health impacts of climate change in general, and for the purposes of this chapter ambient

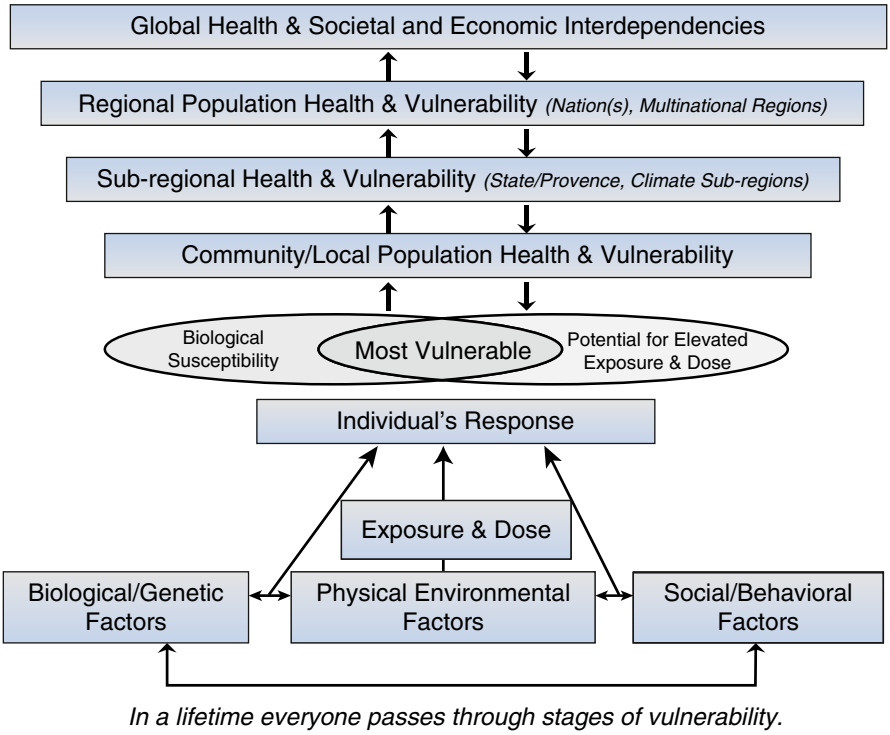
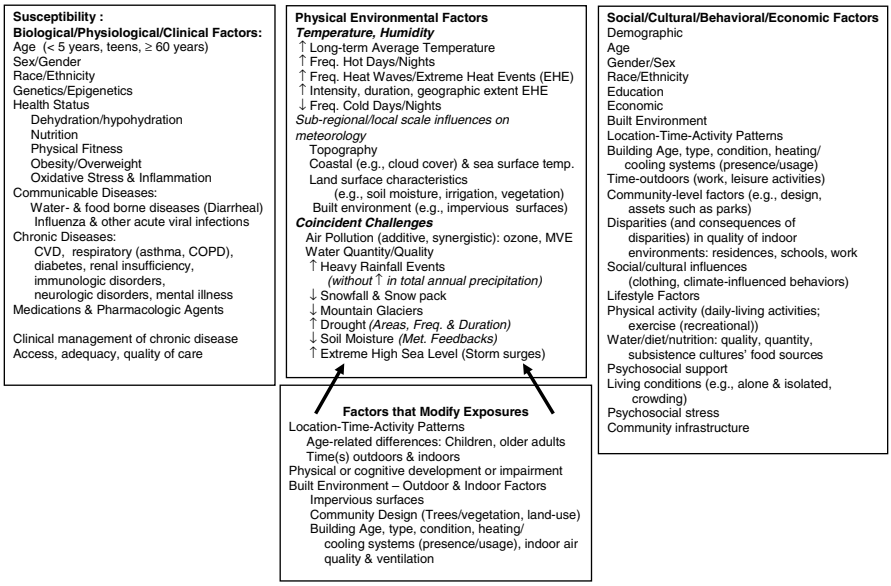


Fig. 6.1 Schematic of the *Environmental Health Multiple-Determinant Model of Vulnerability.* The premise of the model is that, as for most public health issues, there are disparities in how and the extent to which physical environmental factors (e.g., heat, air pollution, water quality/access) impact different populations and subgroups. Further, the health impacts of environmental factors on populations, begins with impacts on individuals, and in a lifetime everyone passes through stages and degrees of vulnerability, with potential lifetime cumulative influences (positive and negative) affecting risk. Vulnerability is greatest among individuals (or subpopulations) who are most biologically susceptible and who have the largest exposure to one or more environmental hazards (depicted by Venn diagram). Vulnerability for development and severity of heat stress/heat strain and subsequent risk of illness or death (whether considering individual risk or population risk), is a function of complex interrelationships among *biologic factors*, including those that confer innate biologic sensitivity and/or resilience to an environmental insult (e.g., sex, race/ethnicity, oxidative stress, nutritional status, comorbidities and related treatments, and genetics/epigenetics); *physical environment and exposure characteristics* (e.g., physical/chemical nature of the exposure, duration and dose, coincident environmental stressors (such as water and/or food scarcity, air pollution)); and the *social, behavioral, and economic factors* that may influence (or be associated with) both biologic response and exposure (e.g., access to healthcare, social isolation, location-time-activity patterns, disparate neighborhood exposure levels)

heat in particular. Vulnerability factors and their relative importance may differ at the individual and population levels and at different geographical scales or geopolitical domains, and there can be cross-scale interactions among factors. Furthermore, the presence and importance of a given factor or factors can change over time,

Table 6.2 Determinants of heat-related morbidity and mortality



affecting one or more scales differently. Table 6.2 lists observed and putative determinants of vulnerability for HRI and HRMM; selected factors are discussed further above.

Biological Adaptations to Heat Stress and Susceptibility and Pathophysiology of Heat Illness

To facilitate the understanding of the potential source of biological susceptibility, this section provides an overview of the normal physiologic responses involved in maintenance of thermal homeostasis (thermoregulation and acclimatization) and cellular adaptations (thermotolerance), and the pathophysiological consequences when the body's heat load exceeds its cooling capacity. It is beyond the scope of this chapter to provide detailed information on the prevention, diagnosis, and treatment of HRI (or of other heat-related morbidity) in the general or vulnerable populations; in addition to authoritative medical texts, that information is available from other sources, including for the general population [47], and for older adults [48–50], infants and children [39, 51–53], athletes [39, 54], the occupationally exposed [55–58], persons with alcohol, drug and mental health disorders [59], and those taking medications (neurologic and non-neurological) [43].

Thermoregulation, Acclimatization, and Thermotolerance

Thermoregulation is a collective of mechanisms, behavioral and physiological, by which humans (and other homeotherms) maintain thermal homeostasis, and avoid development of, or minimize the adverse consequences of *heat stress* (see Table 6.1). *Behavioral Thermoregulation* ultimately aims to reduce exposure by modifying the microclimate (e.g., through clothes, buildings (residence and work), air conditioning) and by modifying location-time-activity patterns. The focus here is on *Physiological Thermoregulation*, which involves integrated biological processes that serve to balance the body's heat gain (from internal heat generated via mechanical work (i.e., physical activity) and basal metabolic processes, and/or gained from environmental heat exposure) and heat dissipation to the environment so as to maintain the core body temperature (T_c). The T_c is the operating temperature of vital organs in the head or trunk and must be maintained in a narrow range 35–40 °C (95–104° F) with an usual target temperature of 37 °C (98.6° F) at rest [1, 2, 4]. For healthy subjects at rest there can be between- and within-subject variation of T_c of up to about 1 °C due to a number of factors, e.g., diurnal fluctuations, menstrual cycle phase, acclimatization to heat, exercise-related fitness level, and age-related differences [2, 4, 60]. For most healthy (unclothed) humans at rest, ambient temperatures of 24–29 °C (75.2–84.2° F) are thermoneutral, i.e., there is no heat transfer between the body and the environment and basal metabolic processes generate sufficient heat to maintain T_c at the target temperature [2, 4]. The summertime ambient temperature range for thermal comfort (i.e., when an individual expresses satisfaction with their thermal environment) is 23–27 °C (73.4–80.6° F) [61].

Heat balance (i.e., where heat gain equals heat dissipation) requires the continuous transfer of energy, most of which is in the form of heat, across tissues within the body, and between the body and the environment; the transfer of heat follows basic laws of thermodynamics and has been well characterized and quantified in terms of the heat balance equation [4, 61]. A simple form of the equation is shown here:

$$S = M_{(b+w)} \pm K \pm C \pm R - E$$

where S = net heat storage (in tissues); M = Metabolic heat production (basal metabolism (b) + mechanical work (w)); K = Conduction; C = Convection; R = Radiation; and E = Evaporation.

There is continuous heat exchange between the body and the environment that can be described and quantified by the Heat Balance Equation. Storage (S) of heat is a function of metabolic heat (M) produced by basal metabolic processes (b) and heat generated by physical activity (i.e., mechanical work (w) of which only a portion of the energy generated is expended on the work itself), the gain or loss of heat through conduction (K), convection (C), and radiation (R), and heat dissipation through evaporation (E). (For an in-depth discussion of the quantitative aspects of heat balance, see Wenger 2002 [4].) The flow of heat is from warmer to cooler media. Within the body, the tissues store the heat, with tissue average temperatures

and capacity to store and transfer heat varying by tissue type. For example, adipose tissue (i.e., fat) has lower heat capacity [62, 63], and its conductivity is about one-third that of muscle, with the rate of heat flow substantially slower (14 kcal/h for fat and 40 kcal/h for muscle) [4]. Convective heat transfer is involved in the flow of heat via the blood from working muscles to the core and from the core to the surface tissues [2, 4]. Conductive heat transfer occurs between tissues that are in direct contact, with the net heat flow from the core to the surface [2, 4]. Heat exchange between the body and the environment is primarily through radiation, convection, and evaporation (most important for dissipation of heat in warm environments) with all three processes occurring at the skin, but only convection and evaporation occurring in the respiratory tract (i.e., air is usually cooler and dryer than exhaled air) [4]. Notably, for a person at rest, radiation (in the form of infrared rays) is the primary pathway by which the body loses heat to the environment; however, the temperature gradient between the skin and the environment influences whether there is heat loss or gain via radiation. Heat gain from solar radiant energy or from solid objects such as paved surfaces can be a significant contributor to heat stress. Conduction usually plays a negligible role in body-to-environment heat transfer; however, it has an important role in treatment of extreme hyperthermia if the patient is immersed in a cool water bath (or shower) to facilitate rapid cooling (with careful monitoring of patient T_c to prevent overcooling) [64]. Clothing can significantly affect heat gain and heat loss (by impeding evaporation and heat transfer) and can be a major contributor to uncompensable heat stress, for example, in occupational workers wearing heavy impermeable clothing [4, 62].

Within a 1 °C rise in blood temperature, afferent heat receptors in the body core and skin transmit signals to the central nervous system's (CNS) primary thermoregulatory centers in the preoptic and anterior hypothalamus, where thermodetectors sensitive to increases in their own temperature trigger an efferent response. That response includes a suite of physiologic processes that ensure adequate energy and oxygen while increasing flow of the heated blood from the core and working muscles to the surface of the body from where the heat can be dissipated to the environment, primarily by an increase in sweating (rate and the number of eccrine sweat glands activated) [4, 65]. (Temperature receptors in other CNS sites (e.g., medulla) also play a role, and there are thermal receptors outside the CNS, (e.g., in heart, and pulmonary vessels) the role of which is not known [4].) Blood flow to the skin is the result of active sympathetic cutaneous vasodilatation. Increased heart rate, cardiac output, and minute ventilation rate facilitate the shift in blood to the body surface [3, 65]. Efficiency of cooling by evaporation of sweat depends on the air velocity and the water vapor pressure gradient between the skin and the air surrounding the body. The greater the water saturation of air the less cooling can occur. For the thermoregulatory response to be sustained, there must be adequate water intake and electrolyte supplementation to offset the losses [3, 4, 65].

Heat Acclimatization and Thermotolerance

Repeated exposure to either passive-heat or exercise-heat stress with attendant increases in T_c leads to physiological adaptations, referred to as *heat acclimatization* (see Table 6.1) that enhance perception of thermal comfort, increase work/athletic performance, and ultimately mitigate risk of heat-related morbidity [1, 66, 67]. There are various definitions of *Thermotolerance* (*aka* thermal or heat tolerance) in the literature; however, as defined by Moseley [67] it is "a cellular adaptation caused by a single severe but nonlethal heat exposure that allows the organism to survive a subsequent and otherwise lethal heat stress." Thermotolerance is associated with the presence (and upregulated gene expression) of families of heat shock proteins (HSP), which protect cells and tissues from initial damage and accelerate repair if damage occurs as a result of heat stress, as well as a variety of other insults [1, 67]. The HSP have different cellular locations and functions that include binding to and processing of denatured proteins, management of protein fragments, maintenance of structural proteins, and chaperone of proteins across cell membranes [1, 67]. Acclimatization and thermotolerance are usually considered separately, however, there is evidence they are related through a shared dependence on the Heat Shock Response [67, 68] or more broadly the Stress Response [67, 69]. In that context, acclimatization can be viewed as a whole organism adaptation, of which thermotolerance—a cellular adaptation—is one part. After exposure to repeated heat-exercise stress, there is a reduction in gastrointestinal barrier permeability (discussed further in section on HRI pathophysiology), and there is an increase in cytoprotective HSP70 along with a decrease in plasma levels of tumor necrosis factor-alpha (TNF-α) and the pro-inflammatory interleukins (IL) IL6 and IL10, leading to lower levels of cellular and systemic markers of heat strain [68]. It should be noted that the complex array of cytokines involved in the systemic inflammatory response syndrome (SIRS) have both a role in promoting and resolving the SIRS [31].

Most of the information on acclimatization in humans is derived from sports physiology or military medicine research on acclimation among young healthy study subjects, usually males, that examined the immediate and/or adaptive physiologic responses from short-term exposures to heat-exercise stress under experimental (i.e., controlled) conditions. Short-term acclimation and acclimatization reflect similar physiologic adaptations that develop (or decay in the absence of heat-stress exposure) over a period of days to weeks [66]. There are very few published studies of long-term acclimatization (or habituation), which occurs over a period of years and reflects both the short-term physiologic adaptations and other usually poorly characterized physiological, behavioral, and technological adaptations by populations and individuals. There is also little published research on acclimation/acclimatization in the general population or vulnerable subgroups, such as the elderly, children, or those with chronic medical conditions.

When acclimatized, an individual's metabolic rate and T_c are lower at rest, accompanied by a lower heart rate, and under conditions of heat stress, there is an

increase in stroke volume and blood/plasma volume, a reduced loss of electrolytes in sweat/urine, and increased thermal tolerance (i.e., cellular stress protein adaptations) [1, 65, 66, 68]. Among the physiologic adjustments that underlie those changes are a lower T_c threshold required for sweating to be initiated and the sweat rate is greater per degree rise in T_c, which enhances evaporative heat loss and the ability to lower skin and core temperatures [4, 66]. Also, skin vasodilatation and core-to-skin heat transfer is initiated at lower T_c and skin blood flow is higher for a given T_c [66]. The physiologic systems involved in acclimatization adapt at different rates, with changes in heart rate and plasma volume occurring first, then the reduction in resting T_c, and finally changes to sweat and sweat rate [66].

The rate of induction of heat acclimatization is exponential with 75 % of the adaptations occurring within about the first 4–6 days of heat-exercise stress exposure and almost complete adaptation present after about 7–10 days [66]. One recommended protocol to achieve acclimatization is a single-daily exposure of about 100 min, with a work rate sufficient to increase T_c to 38.5 °C (101.3° F) [66]. Moseley [67] has noted that passive heat exposure-induced hyperthermia is usually associated with only partial acclimatization. Once heat acclimatized, unless there is repeated heat-exercise or passive heat exposure(s), there is a decay in acclimatization that can occur in as little as a week, with the decline in the different physiologic systems' adaptations occurring in reverse order of induction [66]. Depending on the interval without exposure to heat stress, re-acclimation is more rapid than initial acclimation. There is far less research on the time course of acclimatization decay and re-acclimatization or the determinants of those rates. One rule of thumb has been that for every 2 days without to heat stress exposure, there is 1 day of acclimatization lost; however, more recent research suggests that decay occurs more slowly and that at least for healthy young adults they can safely return to work or athletic competition after as long as a month away from heat stress conditions [66].

Adaptations associated with thermotolerance, i.e., the HSP response, are evident within several hours of heat stress exposure (messenger RNA levels peak within the first hour) and increase for several days [1, 67]; however, the duration of the adaptations is only for 2–7 days (in contrast to acclimatization which is indefinite as long as a person has periodic mild elevations in T_c) [67]. After the initial exposure, HSP synthesis is a function of the intensity, duration, and cumulative effects of subsequent heat-stress exposures [1]. Importantly, although passive heat exposure and physical exercise can independently trigger HSP synthesis, there is a greater HSP response when those two stressors are combined as compared to either one alone [1].

It is important to emphasize that, although there is a paucity of data for the general or vulnerable populations, it is known that the time required to acclimatize or to see significant decay in acclimatization and to re-acclimatization can vary substantially depending on an individual's age, health status (especially by physical fitness, obesity (adiposity), or cardiopulmonary diseases), and the type of exposure (i.e., passive heat or heat-exercise exposure).

Heat Stress-Related Morbidity and Pathophysiology of Severe Heat-Related Illness

Any individual, regardless of age, sex, or health status, can develop heat stress if engaged in intense physical activity and/or exposed to environmental heat (dry or humid), especially if they are not acclimatized. If heat stress exceeds the physiologic capacity to cool and T_c rises, then a range of heat-related symptoms and conditions can develop. The medical conditions that result from heat stress/heat strain and fall within the formal classification of *Heat-Related Illness* (HRI) represent a spectrum that starts with relatively mild and easily treated illness (heat cramps, heat edema, and heat syncope) and progresses in severity to heat exhaustion and then to heat stroke, an extreme medical emergency. While the mild conditions may not be life threatening, to prevent progression to more serious HRI, they should be treated appropriately and taken as warning signs to immediately remove an affected individual from the exposure situation. Table 6.3 provides an overview of the milder forms of HRI; the focus below is on the most severe condition—heat stroke.

Table 6.3 Heat-related illness: heat cramps, heat edema, heat syncope, and heat exhaustion[a]

Heat cramps: severe painful cramping of muscles in the legs or abdomen are the hallmarks of heat cramps, which result from electrolyte disturbance, most notably when plasma sodium levels fall significantly below normal. Heat cramps are commonly caused by exertion, with profuse sweating, and often occur during cool down after activity has stopped. Stopping intense activity and consumption of drinks with electrolytes (e.g., some sports drinks) to replenish fluid volume and electrolytes is usually sufficient treatment
Heat edema: *s*welling in the legs due to accumulation of fluids in the tissues; results from prolonged dilatation of the small arteries in the legs, especially after prolonged standing or sitting still in the heat. Treatment is to increase circulation (venous return) by alternating between elevating the legs and gently moving them
Heat syncope: sudden loss of consciousness (fainting), usually preceded by light-headedness or weakness, can result from orthostatic hypotension related to peripheral blood pooling. Loss of consciousness can be prevented by sitting or lying down at the initial signs of illness (dizziness, weakness)
Heat exhaustion: extreme depletion of blood plasma volume, which may be coincident with low plasma levels of electrolytes, as well as peripheral blood pooling, can lead to heat exhaustion. Core temperature may be in the normal range or slightly elevated but less than 40 °C. Symptoms can include generalized malaise, weakness, nausea, vomiting, headache, tachycardia, and hypotension. Although there can also be mild disorientation, the absence of clear neurologic complications distinguishes heat exhaustion from heat stroke
If heat exhaustion is suspected, the recommended course of action is to immediately move the affected individual to a cool environment and give them fluids supplemented with electrolytes. It may be necessary to actively cool the person by loosening clothing, increasing air flow across the skin, for example with a fan while misting or wiping them down with cool water, or placing ice packs on their extremities. Massage of extremities to mitigate vasoconstriction associated with use of cold water or ice is usually recommended

[a]Heat stroke is the most extreme form of HRI and is discussed in main text

Heat Stroke

Heat exhaustion may be the early stage of heat stroke [54], and within a 24-h period if untreated, it can progress to heat stroke; thus, to prevent heat stroke and improve patient outcome, treatment should begin at the first signs of heat exhaustion. Heat exhaustion does not necessarily present with definitive symptoms, therefore it is frequently misdiagnosed, commonly as acute viral infection, leading to delayed treatment. Importantly, acute viral or bacterial infections coincident with heat stress are implicated in increased risk of heat stroke [31], as well as sudden infant death syndrome (SIDS) in infants who were also more heavily wrapped in clothing [70]. Heat stroke is typically divided into two types: "Exertional Heat Stroke" as the name implies involves strenuous physical activity usually under high temperature conditions to which the person was not acclimatized and usually affects healthy older teens and young adults, such as athletes, occupational workers, and soldiers. "Classic heat stroke", by definition, does not involve exertion and usually affects biologically susceptible individuals, such as infants and young children, the elderly, persons with chronic illness and/or taking medications (prescribed or over-the-counter), as well as persons with alcohol or drug dependencies and with mental illness or neurologic conditions [43, 59]. It is imperative that measures be taken to prevent and/or aggressively treat heat stroke, which, even if treated, can have a crude mortality rate as high as 50 %, and a large proportion of heat stroke survivors suffer permanent neurologic damage [3, 71]. Among 58 survivors of near-fatal classic heat stroke that occurred during the 1995 Chicago heat wave, 33 % had substantial functional impairment at discharge from the hospital and had not improved at 1-year follow-up [71]. The sequelae of heat stroke-related multiorgan system dysfunction/failure (discussed below) can persist months or years after the initial treatment thereby increasing the risk of mortality over the long term [31].

For both types of heat stroke, the clinical definition is when a person's body core temperature rises above 40 °C (104° F) and there are CNS neurologic complications (e.g., initially headache, dizziness, and weakness followed by hallucinations, combative behavior, coma, and seizures) [3, 31]. The more quickly the patient receives treatment to bring down their T_c to 39 °C (102° F) or below (ideally within 30 min of presentation [71]), and supportive therapies such as replacement of blood volume and electrolytes are administered, the less likely are severe complications and the better the prognosis [3, 31]. Although the clinical criteria and overall treatment of both types of heat stroke are essentially the same, a number of differences in patient characteristics, including signs and symptoms have been noted [65] that reflect the population subgroups commonly affected and that may require medical interventions specific to their unique physiology and medical status. For example, in classic heat stroke sweating is usually absent, respiratory alkalosis is a dominant feature, coagulopathies (i.e., disseminated intravascular coagulation (DIC)) is mild, and if present rhabdomyolysis is rarely severe, whereas in exertional heat stroke sweating is often present, respiratory alkalosis is mild, DIC is marked, and rhabdomyolysis is severe [65].

Heat-Related Illness: Pathophysiology

Over the past 2 decades, research has led to critical insights to the pathophysiology of heat stroke [3, 31, 65]; based on that information, Bouchama and Knochel (2002) proposed that heat stroke be defined as *a form of hyperthermia associated with a systemic inflammatory response leading to a syndrome of multiorgan dysfunction in which encephalopathy predominates* [3]. It has long been known that heat stroke is associated with an overload of the thermoregulatory response, including reduced capacity to increase cardiac output due to water and electrolyte depletion, cardiovascular disease, or medications or alcohol and illicit drugs, that affect cardiovascular, respiratory, or neurologic function [3, 43, 59]. As the T_c rises above 40 °C (104° F), there is tissue injury, with the extent of injury a function of the level and duration of heating [3]; the acute injury triggers the acute phase response (APR). It is now recognized that an upregulated APR and oxidative stress (likely both a precipitant and a downstream consequence of the APR) and possible altered expression of cytoprotective HSP are central to the pathophysiology of heat stroke [1, 3]. The cytotoxic effects of heat and the APR-associated inflammatory and coagulation responses of the affected individual contribute to the multiorgan injury [31]. As noted above, as part of the normal thermoregulatory process in response to hyperthermia, i.e., increased T_c, the circulation of blood is shifted to the skin and working muscles and away from vital organs, including the gastrointestinal tract; this can lead to ischemia of the gut and intestinal hyperpermeability. An emerging body of evidence, primarily from animal models, indicates that endotoxemia resulting from intestinal hyperpermeability and leakage into the circulation may contribute to the progression from heat stress to heat stroke [1, 3, 31, 65].

Within the scope of this chapter, it is not possible to review the literature on this critical line of investigation linking heat stroke and the heat-stress response, oxidative stress and systemic inflammation, and the complex interplay between the innate and adaptive immune systems' responses (see Leon and Helwig for an overview [31]). However, it is important to note that over the past 2 decades a robust body of evidence has linked systemic and/or organ-/tissue-specific inflammation and oxidative stress pathways to: aging [72]; to the pathophysiology underlying a number of chronic diseases and related conditions (e.g., atherosclerosis and cardiovascular disease) [73, 74], chronic respiratory disease (e.g., asthma and chronic obstructive pulmonary disease (COPD)) [73, 75, 76], diabetes and obesity [77, 78]; and as potential mechanisms by which ambient air pollution increases the risk of acute exacerbations of those chronic diseases/conditions and/or contributes to their development and severity [79–84]. Furthermore, oxidative stress may impair the protective heat shock response [30], potentially reducing thermotolerance and increasing risk and severity of heat stroke. The implication of these observations is that individuals with chronic health conditions/diseases who already have high levels of oxidative stress and chronic inflammation are at elevated risk of HRI [31], and that this is an important underlying mechanism that contributes to the excess acute

cardiovascular, respiratory, and diabetes cases associated with ambient heat. This will be an important area of further delineation and research, as it also opens the door to many more clinical and public health intervention options.

Vulnerable Populations: Determinants of Thermoregulatory Capacity

The strongest and most consistent observations in epidemiologic studies have been an elevated risk for HRMM among older adults, children, and people with chronic diseases regardless of age. There are physiologic attributes specific to older adults and children that affect thermoregulation (described below); however, recent literature suggests age per se is not in of itself necessarily the major driver of risk, but rather it is the common (often interrelated) correlates of age specific to these age groups that contribute greater risk. Some of these factors are shared determinants of risk (SDR), i.e., factors that impact these and other population subgroups.

Older Adults

Under resting thermoneutral conditions, older men and women have been reported to have lower T_c than younger adults; however, after accounting for factors such as nutrition, comorbidity, and medication effects, the differences in T_c related to age essentially disappear [49]. The number of sweat glands and sweat gland function, in particular the amount of sweat produced per gland, diminishes with aging [49]. Sweating rate of older adults has been reported to be diminished under passive heat exposure; this appears to be a function of maximal oxygen uptake (VO_{2max}; a measure of aerobic capacity) rather than chronological age [49]. Chronological age-related reductions in skin blood flow do occur (attributed to reduced superficial microvasculature), accompanied by lower cardiac outputs and less redistribution of blood flow from the splanchnic and renal circulations [48, 49], with some yet to be understood sex differences in the central cardiovascular changes observed under conditions of heat stress [49]. Overall with age there is potential for greater heat gain and a diminished capacity for heat dissipation, especially via evaporation, as a result of the changes to sweating capacity and cardiovascular function noted above and an increase in body mass (and associated increase in adiposity). The greater the body mass, the more heat is generated for a given activity level [48], and the smaller the surface area to body mass ratio so cooling capacity is diminished. In addition to adipose tissue acting as insulation and impeding heat exchange, there are less heat-activated sweat glands found in skin covering adipose tissue [48]. Importantly, with aging peripheral and central thermosensor neurons are less sensitive and respond less effectively to temperature changes, with the result that elderly have a decreased perception of heat along with less effective heat dissipation mechanisms [48], which together has important implications for HRMM risk and prevention.

A number of chronic medical conditions disproportionately affect older adults and predispose them to heat illness.(48) Cardiovascular disease is the most important, with direct effects on thermoregulatory mechanisms and capacity, e.g., heart failure and myocardial infarction affect cardiac output and potentially cutaneous vasodilatation. Atherosclerosis, hypertension, and type II diabetes mellitus reduce vascular compliance and can directly affect thermoregulatory capacity [48]. Chronic respiratory diseases, such as COPD and asthma, can impair thermoregulatory capacity (due to diminished ability to provide sufficient oxygen to support increased energy demands) and contribute to hypoxemia that amplifies tissue damage and the risk and severity of heat stroke. Reduced fluid and electrolyte retention and dehydration are associated with aging-related renal insufficiency and with diabetes (type II diabetes mellitus, diabetes insipidus)-related renal damage and impaired renal function. Hypohydration and dehydration are common among older adults, who in addition to changes in renal function also experience a decreased sense of thirst, or to manage bladder control problems they (or their caregivers) may limit their fluid intake [50]. Obesity and/or lower lean body mass are common among the elderly, and as described above can directly affect thermoregulation and risk of HRI. And as noted above, cardiovascular and respiratory diseases, diabetes, and obesity/overweight are associated with elevated oxidative stress and chronic inflammation, which can contribute to pathophysiology and risk of heat stroke. Hyperthyroidism (via increased metabolic heat production or hyperpyrexia), and extensive skin damage or disease, can also directly affect thermoregulatory mechanisms [48]. Neurologic and psychiatric disorders that disproportionately affect older adults may directly impact CNS thermoregulatory centers and efferent responses and/or contribute to behaviors (e.g., wearing excess clothing or not removing themselves from excessive heat exposure) and social conditions (e.g., being socially isolated) that increase the risk of HRI [48]. A point of concern for the elderly, and an area that has not received much consideration in the context of direct or indirect influence on HRI, is nutritional deficiencies, such as inadequate intake of antioxidant-rich foods. Many of the above conditions occur concurrently, with complex physiologic and clinical interrelationships, including treatment and disease management that further complicates delineating a clear path to HRI risk prevention strategies. For example, recommendations to increase fluid intake to prevent hypohydration/dehydration may be contraindicated for a person with heart failure or with renal failure on hemodialysis. Medications may play a critical role in altering risk for HRI [43, 59]. While the literature focuses on increased risks of HRI and HRMM associated with commonly prescribed or over-the-counter medications, there may also be protective effects afforded by medications, such as anti-inflammatory agents.

Infants and Children

A number of studies point to increased risk of HRMM among children, especially those less than 5 years of age [14, 41, 85] and adolescent athletes [86]. Heat stroke is the third leading cause of death among high school athletes in the United States [86].

Most of the information on heat stress and HRI in children is in the context of exercise and physical activity, which by default focuses on school-aged children (e.g., ≥5 years of age). Despite the epidemiological evidence pointing to infants and very young children being at especially high risk, there is a paucity of literature that discusses thermoregulation or risk factors (other than extreme exposures such as being left in a car) for HRI in this age group, especially infants. There is a rich literature on hypothermia in neonates and on SIDS. From birth through age 3 months, an infant's metabolic rate increases, the ratio of body mass to surface area increases, and at 3 months there is a thicker layer of subcutaneous fat which together shifts thermal balance towards heat conservation [87]. Some research on SIDS has pointed to a combination of ambient heat and concurrent viral infection in conjunction with excess covering (e.g., blankets or clothing), especially of the head where 40 % of heat production and 85 % of heat loss occurs in an infant in bed (elevated head/brain temperature could affect thermoregulation and respiratory control); the risk of SIDS was greater in infants older than 2–3 months as compared to those younger [70, 87]. It was suggested that an increase in metabolic rate associated with viral infection in the older infants reflected an acute phase response, which would not be as well developed in some younger infants [70].

There are physiological differences between children and adults, including morphologic, metabolic, cardiovascular, and sweating capacity that traditionally have been viewed as conferring less thermotolerance and greater risk of heat stress and HRI among children [52, 88]. Children (past early infancy) have a higher body surface to mass ratio which can increase heat gain from the environment (when ambient temperature is greater than skin temperature), and depending on the water vapor pressure of the air (or humidity) evaporative cooling by sweating may not be sufficient to compensate for that gain. Younger children are less metabolically efficient when walking or running such that their oxygen consumption and heat production is greater than that of adults engaged in a similar level of activity, thus potentially increasing heat strain. (This is less of a factor for non-weight-bearing exercises such as cycling or rowing [52]). When children are exercising in heat, heat convection to the body surface (and cooling) may be compromised (relative to similar heat loads in an adult) as a result of the combined cardiac output demands of working muscles and of moving blood to their larger body surface area. Under similar conditions of ambient heat children have a higher skin blood flow (and peripheral vasodilatation), which compromises venous return and in turn cardiac output and potentially thermoregulation and/or exercise performance. The greatest difference between children and adults is their sweating rates (absolute, relative to body surface, and per gland), and there are apparent sex differences, with lower sweat rates more pronounced in boys compared to men, than in girls compared to women [52]. Children also take longer to acclimatize than do adults [53].

Based on recent research, it has been suggested that due to compensatory mechanisms children's thermoregulatory capacity may be more similar to adults than traditionally accepted, at least under less extreme environmental conditions [52, 89]. This position has been adopted in the 2011 revised American Academy of Pediatrics Council on Sports Medicine and Fitness and Council on School Health Policy

statement-Climatic Heat Stress and Exercising Children and Adolescents [89]. A number of risk factors for exertional HRI (heat exhaustion and heat stroke) other than age-specific differences in thermoregulation were identified, including: current or recent illnesses that alter hydration status or thermoregulation (e.g., gastrointestinal illness and/or fever); chronic clinical conditions (diabetes insipidus, type II diabetes mellitus, obesity, juvenile hyperthyroidism (Graves disease), and cystic fibrosis); medications (e.g., dopamine-reuptake inhibitor to treat attention deficit/hyperactivity disorder or enhance performance, or diuretics); any other acute or chronic medical condition or an injury that affects water-electrolyte balance, thermoregulation or exercise-heat tolerance; and lastly Sickle cell trait, which can contribute to risk and severity or complications of HRI [89].

Chronic respiratory diseases (allergic airways diseases and asthma), and obesity and associated with it type II diabetes mellitus have reached epidemic proportions among children, especially in developed nations. (In developing nations obesity is also epidemic; however, there are complex interrelationships between malnutrition in children and obesity in adults [90]). The pathways by which these conditions can amplify risk of HRI or HRMM in children are for the most part the same as noted above for the general population and older adults and will not be revisited here. However, in the context of climate change and the projected increases in ground level ozone (a potent oxidant), it is also important to note that children are especially vulnerable for developing chronic respiratory disease. They are biologically more susceptible due to their developing respiratory tracts and immune system, and they have potential for greater exposures and doses of air pollution as their breathing rates relative to body size are greater than adults, and they spend more time outdoors. In a cohort of children in southern California, participation in three or more team sports (an indicator of intense physical activity outdoors) in communities with high ozone was associated with a threefold higher risk of developing new onset asthma, as compared with children playing no sports. No effect of sports was observed in low ozone communities [91]. In another study of children with asthma, anti-inflammatory medication was observed to modify (diminish) the effect of air pollution on asthma symptoms [92]. There is also accumulating evidence that dietary intake of antioxidants (e.g., vitamin C), and specific genetic polymorphisms that are associated with antioxidant capacity, independently and/or jointly can modify the effects of ozone on children's lung function and growth [93, 94].

Determinants of Thermoregulatory Capacity: Additional Population Subgroups

Sex/Gender

Epidemiologic studies have yielded heterogeneous results when sex/gender is considered as a risk factor for HRI or HRMM. Most past research on thermoregulation has been in young healthy men and has not explicitly examined

thermoregulation in women or sex-related differences in men and women. A review by Kaciuba-Uscilko and Grucza [60] concluded that *despite a smaller sweating response to heat load in women than in men, there are no substantial sex differences in the effectiveness of thermoregulation, except those that resulted from differences in body size and composition and physical working capacity*. They noted there were sex-hormone-related fluctuations in body temperature and some thermoregulatory processes during the menstrual cycle and in menopause; however, the mechanisms by which sex hormones affect thermoregulation require further study. To the extent there is differential distribution of predisposing chronic conditions/diseases or that lifestyle factors and location-time-activity patterns differ among men/boys and women/girls, the impacts of ambient heat and risk of HRMM would be expected to differ.

Race/Ethnicity

A review of temperature regulation and ethnicity by Lambert and colleagues (2008) [95] provides insights to variation in physiological traits across human populations that developed over the long term as a function of different climatic conditions. They noted the evidence suggests the differences reflect phenotypic rather than genotypic variation [95]. As in the case of sex-related differences in risk, differential distribution of predisposing chronic conditions/diseases across race/ethnicities also would affect the impacts of ambient heat. Disentangling the complex relations between physiological and morphological characteristics (and potentially the underlying genetics) that affect thermoregulatory capacity in warm/hot climatic conditions, from the social, behavioral, economic, and environmental determinants of health that affect overall health (resiliency) and risk of HRI and/or HRMM poses significant challenges. There are both challenges and research opportunities afforded by the increasing ethnic diversity of many nations resulting from modern migrations facilitated by population mobility.

Genetics/Epigenetics

Research on genetic polymorphisms and epigenetic processes that modulate (increase/diminish) susceptibility to physiological heat stress, oxidative stress, and/or the heat shock response associated with environmental challenges (e.g., heat, air pollution, toxins) or specific diseases/conditions and subsequent risk and severity of heat illness are areas of intense investigation [96, 97]. This research offers future promise of identifying the most at-risk individuals and subpopulations to target interventions for prevention. It may also provide more definitive insights to a biological basis for observed variation in risk of HRMM among different race/ethnic groups or between females and males.

Global Environmental and Societal Challenges Affecting Population Vulnerability

Global warming, in addition to increasing land surface average temperatures and frequency of EHE that are of greater intensity and duration [5], will also lead to other concurrent environmental changes, such as increased occurrence of droughts and extreme precipitation events, to sea level rise and higher storm surges, and to higher levels of air pollution, most notably ozone [6], the independent and joint effects of which will significantly affect the ability of ecosystems and human populations to cope with changes in temperatures. From a global health perspective, the most important coincident challenge will be hydrological system perturbations and downstream consequences on water and food security, and energy production and distribution (e.g., due to infrastructure damage), which have direct and indirect impacts on individuals', populations', and societal adaptive capacity. Of critical importance is that not only will there be coincident challenges to health within a given region, there is mounting scientific evidence that synoptic climatic processes are leading to coupled extreme weather events in distant regions. For example, EHE and extended droughts in Russia have been climatically tied to extreme precipitation events in Pakistan [98]. Among the effects these extreme weather events have locally are impacts on water availability and quality, and on crop production. A related concern is there is high confidence that many semiarid areas (e.g., the Mediterranean Basin, western United States, southern Africa, and northeastern Brazil) will experience decreased water resources [6]; many of these areas are among the most productive agricultural regions globally. Thus, not only is water and food security impacted within each affected region, the overall capacity for the international community to provide aide to any one region is diminished due to multiple regions being affected and potentially needing aide at the same time.

While global warming discussions usually note average *global* increases in temperature (land and ocean), at the local and subregional scales (e.g., subcommunity, community), there exist large variations in land surface temperatures—averages and excursions above averages (variability), and with climate change the degree to which temperature will increase in a given location will also vary and not always predictably. For example, climate models predict that year-round average temperatures throughout California will keep increasing with warming more pronounced in the summer than in the winter season, and depending on the general circulation model (GCM) and greenhouse gas (GHG) emissions scenario, the summer (July–September) increases range from 1.5 to 6 °C (2.7–10.8 °F) [99]. Also predicted is greater warming in inland areas, as compared with coastal locations (within ~50 km of the coast) with the increase as much as 4 °C (7.2 °F) higher in the interior land areas as compared to the coast [99]. As elsewhere, the frequency, intensity, duration, and geographic extent of EHE are predicted to increase in California; a trend already evident in the past decade along with the emergence of EHE characterized by higher humidity and higher minimum (overnight) temperatures [10]. Urbanization/suburbanization accounts for areas with the largest increases; however, there are also

many rural areas that have experienced substantial temperature increases [99, 100]. That noted, the urban heat island effect can contribute to ambient temperatures being more than 10 °C higher than neighboring rural areas. Among the factors that contribute to this phenomenon is greater heat generation from local sources such as vehicles and other machinery; dark surfaces with low albedo (i.e., reflectivity) that absorb and reradiate heat; low vegetation density and commensurate reduction in capacity to cool through evapotranspiration; and layout and design of buildings and other structures (e.g., urban canyons, height) that result in heat retention [101, 102]. Interestingly, independent of climate zone, metropolitan population size or rate of metropolitan population growth, over the last half century the rate of increase in the annual number of EHE was reported to be greater in metropolitan regions characterized by greater urban sprawl compared with more compact metropolitan regions [101]. The primary mechanism attributed to this observation was the rate of deforestation in more sprawling areas and the associated loss of regional vegetative land cover [101].

Human populations are not just facing unprecedented environmental changes but also global societal and demographic shifts. Key among the societal changes is the migration from rural communities to densely populated urban locations where in addition to higher temperatures there are other challenges to health [103]. In developing nations, migrants tend to be poor and frequently end up in "irregular settlements" where there is little or no heath protective infrastructure such as sewer systems and reliable potable water sources [29, 104]. In these settlements, as well as many other urban and rural communities in developing nations, water- and foodborne diseases, especially diarrheal diseases among infants and children under 5 years of age, remain a leading cause of illness and premature preventable deaths, despite the eradication and improved management of many communicable diseases that have been achieved globally [105]. Even in developed nations, populations that are economically disadvantaged (and/or medically underserved) or displaced (e.g., due to natural disasters) are also at elevated risk of communicable diseases, as was seen in the aftermath of Hurricane Katrina in the United States [106]. Diarrheal and other communicable diseases, including intercurrent infections, can predispose affected individuals to heat stress and HRMM [3, 71, 89]. Wherever populations reside, work, or recreate, insufficient access to potable water increases the risk of hypohydration and dehydration and in turn to increased risk of heat stress and HRMM in general and HRI in particular.

Strategies to Reduce Vulnerability and Incidence of Heat-Related Morbidity/Mortality

As noted at the beginning of this chapter, the existent and projected large public health and healthcare burden associated with ambient heat requires that the emergency response approach to EHE be augmented with strategies that reduce individual and population risk of HRMM over the full range of ambient heat

conditions. Effective policies and interventions require knowledge, not assumptions about who is at risk, the drivers of that risk, and where and when those determinants of risk are greatest, as well as the efficacy of risk-reduction strategies. Within the framework of an Environmental Health Multiple-Determinant Model of Vulnerability (Fig. 6.1; Table 6.2) that incorporates knowledge from different disciplines, it is possible to identify the factors that independently or jointly confer increased (or diminished) risk of HRMM within the general population and within or across specific subpopulations already identified as *vulnerable*. In addition to developing/implementing evidence-based *Extreme Heat Event and* W*arm Season Heat Preparedness and Response Action Plans*, two other overarching and interrelated strategies are self-evident: *Promote Good Health & Access to Quality Healthcare* (*reduces risk and increases resiliency*) *and Reduce/Manage Potential Exposure*(*s*) (*individual*, *community*) *to Ambient Heat and Other Physical Environmental Stressors*. To be efficacious and resource-efficient, all three strategies require a coordinated "top-down" and "bottom-up" approach involving governments, nongovernmental organizations, communities, and strong partnerships with diverse stakeholders (e.g., public health officials, healthcare and social service providers, educators, athletic coaches, and other private sector participants such as faith-based organizations). The translation of those broad strategies to specific actions is where careful integrative considerations of the multiple determinants of risk becomes most critical, and the implementation is most challenging, especially in light of climate change-related environmental shifts. The discussion below primarily focuses on examples of translation and integration in the context of the two overarching strategies and heat-health action plans.

Promote Good Health and Access to Quality Healthcare

The above overview of normal thermoregulatory processes, pathophysiology of severe HRI (heat stroke), and the characteristics of older adults and children that affect their risk for HRMM highlighted key points of knowledge. Most notably, the recurrent theme for both age groups (with special considerations for infants) and applicable to other age groups is that individuals (females and males) who are more physically fit, have greater percent lean body mass, are adequately hydrated, and are not afflicted with a chronic disease (especially cardiovascular, respiratory, neurological, renal, or diabetes), and do not have an acute intercurrent infection, are less biologically susceptible to HRI and HRMM because they have the physiological reserves to experience moderate-to-extreme heat stress and heat strain and still maintain thermal homeostasis, with less cell and tissue damage, and low risk of acute cardiopulmonary events or other complications of heat strain. In addition, physiological acclimatization can further reduce susceptibility and enhance resilience to heat stress/heat strain. Although far from being fully elucidated in the context of the sequelae from heat stress to heat exhaustion and heat stroke, a biological mechanism that unifies these observations in the healthy heat acclimatized

phenotype is a lower level of oxidative stress and less chronic low-grade inflammation and potentially modulation of the acute phase response and stress response (e.g., downregulation of pro-inflammatory cytokines and upregulation of HSP response) that together confer greater thermotolerance. Beyond thermotolerance there may be important co-benefits of enhancing the HSP response. HSP have the potential to alter obesity-induced insulin resistance (via preventing inflammatory disruption of insulin signaling), and lower HSP expression has been observed in human diabetes patients [78]; thus maintenance of HSP expression may be a pathway by which insulin resistance and diabetes are or could be improved with exercise [78] (and potentially exercise-heat acclimatization protocols).

Thus, the broadest recommendation to diminish HRMM across an entire population over the long term, with near-term benefits, is to invest in and capitalize on public health programs and interventions that aim to improve health and prevent/manage common chronic diseases, especially through improved nutrition and increased physical activity, as well as prevent/manage communicable diseases with specific consideration of the impacts (e.g., via dehydration, fever) on risk of HRMM. Integral to achieving that overall aim is to ensure access to healthcare (especially preventive medicine), and ensure clinicians and other healthcare service providers or points of patient contact (e.g., pharmacists) are informed about the HRMM risk factors relevant to their patients and measures that can be taken to manage that risk. This approach can contribute significantly to reducing the pressures on the public health infrastructure created by the global demographic trend towards older populations, and the global increase in prevalence of chronic diseases and obesity, as well as climate change.

Reduce/Manage Potential Exposures to Ambient Heat and Other Physical Environmental Stressors

Achieving “good health” and reducing HRMM, especially as the climate changes, will require concurrently addressing physical environmental stressors. In addition to advocating for and investment in pollution prevention programs at all geopolitical scales, specific actions need to be developed/implemented to reduce potential exposures (to heat, chemical and/or infectious agents) experienced by populations and individuals at the local scale. For example, when making the recommendation to increase physical activity (e.g., to manage weight), assuming the majority of the population does not have options to exercise in indoor locations (with healthful environmental conditions), there also has to be guidance on minimizing exposure to ambient air pollution, which can vary substantially temporally (e.g., diurnally and seasonally) and spatially at the local scale (e.g., neighborhood-to-neighborhood, proximity to a roadway), as well as provide advice to avoid the hottest time of the day (which usually is also coincident with the highest ozone levels). If the individual has compromised health, even if an apparently relatively benign condition such as

being overweight (but not obese and with no other health problems), or if they are taking medications that predispose them to heat stress/heat strain, they need to be alerted to their potentially heightened susceptibility to heat strain and risk of HRI or HRMM. Warnings to acclimatize before engaging in outdoor physical activities need to be accompanied by specific guidance on how to acclimatize. Such guidance is available for athletes (e.g., see Bergeron [89]); however, few if any of the documents that recommend acclimatization specifically address the issue of co-exposure to air pollution or aeroallergens. Currently there is little or no published quantitative information that specifically outlines or provides the basis for acclimatization protocols (that consider both exercise-heat exposure and passive heat exposure) for the general healthy population or subgroups defined by age and/or specific health conditions. This is an area of investigation that should be a priority.

Access to an air-conditioned cooler environment has consistently been associated with lower risk of HRMM over usual summertime and extreme heat conditions [22, 27, 71, 107, 108]. And during EHE, recommendations to use air conditioning or move to an air-conditioned location, including public access cooling centers, have become a cornerstone of HRMM prevention strategies. There are however a number of potential pitfalls to this strategy. Even in developed nations, the energy generation and distribution infrastructure may not be able to support energy demands during EHE of long duration and large geographic extent, especially if there is increased penetration of AC into homes and businesses. During the 2006 California heat wave that also affected other western states (that can share energy resources with California), there were near failures of the power supply, with some areas experiencing brownouts. If there are coincident extreme weather events such as hurricanes or storm surges, the energy infrastructure, including power plants, is at risk. In consideration of climate change and the need to reduce GHG emissions, unless sufficient (truly non-polluting) "green energy" is available, reliance on air conditioning may be counterproductive for health in the near and longer term. Public gathering places, such as older schools or workplaces, and eldercare residential facilities often do not have air conditioning, even in developed nations. Many populations (e.g., in irregular settlements) or individuals within populations (e.g., urban or rural poor in older residences) do not have nor is it feasible for them to have and/or use an air conditioner. A related concern is that the recommendation to avoid heat exposure by going indoors is not universally protective due to highly variable indoor heat and air quality conditions. Furthermore, by avoiding any heat exposure, the opportunity for acclimatization is diminished.

With respect to recommendations to minimize heat exposure, a critical caution regarding the use of fans is warranted. It is not recommended to use fans to prevent an individual from becoming overheated under certain climatic conditions of high humidity (greater than about 33 % relative humidity) and high temperatures (i.e., temperature is ≥32.3 °C (90° F)); when temperatures are above 37.8 °C (100° F), fans may actually contribute to heat stress and subsequent illness (37). However, the use of a fan in conjunction with wetting down the skin of a person showing signs of heat stress or illness can facilitate evaporation and the cooling process.

Clearly, completely abandoning air conditioning as a solution for HRMM prevention is not recommended or feasible. However, more sustainable strategies that focus on reducing heat exposure by modifying the built environment to minimize heat gain (inside buildings and outside) and maximize heat loss and transfer from inhabited areas can reduce the need for air conditioning. Increasingly national and provincial municipal governments are developing/implementing sustainability policies and plans that include improved community design and land-use planning (e.g., increase green space, and rerouting of traffic to decrease vehicle miles traveled), retrofitting existing buildings (e.g., with green roofs, energy efficient windows), and replacing pavement with pervious surfaces. In addition to reducing temperatures (and potentially air pollution exposures), many of these strategies also promote increased physical activity and positively enhance the psychosocial environment and livability of a neighborhood and community and ultimately improve overall health [109].

Extreme Heat Event and Warm Season Heat Preparedness and Response Action Plans

Formal EHE emergency response plans developed and implemented by government organizations at the national, regional, and local levels can significantly reduce HRMM. Comprehensive guidelines and considerations for designing and implementing heat-health action plans focused on emergency response to EHE have been developed by the WHO (Europe) [110]; the guidelines include principles and core elements (summarized in Table 6.4) of a potentially optimum system to prevent EHE-related HRMM that can be adapted to different geopolitical scales and infrastructures. Rather than reiterating recommendations contained in that document, the focus here will be on some of the issues related to enhancing HRMM risk-reduction plans to improve their efficacy during EHE, as well as potentially extending their application to an entire warm season.

The particular issues were identified after the 2006 California heat wave, when the State's Contingency Plan for Excessive Heat Emergencies was reviewed by officials and scientists from public health and emergency response organizations and the US National Oceanic and Atmospheric Administration's National Weather Service (NWS) with the aims to improve heat alert system(s) and emergency preparedness and response, including medical resource planning, and the public health messages and interventions especially those targeted to vulnerable populations. Key gaps in information and limitations in prior studies upon which those systems are based were identified. Among the major issues raised during the evaluation was the need for local scale (i.e., subcommunity such as neighborhood or US census tract) environmental and population data, and two key questions regarding criteria for issuance of heat alerts, including: (1) *Should the definition of a heat wave and heat alert criteria be based on morbidity rather than mortality-response studies as*

Table 6.4 Principles and core elements of heat-health action plans as delineated by the World Health Organization[a]

Principles
• Use existing systems and link to general emergency response arrangements
• Adopt a long-term approach
• Be broad (i.e., emergency response requires multiagency and multi-sector participation)
• Communicate effectively
• Ensure that responses to heat waves do not exacerbate the problem of climate change
• Evaluate (a key public health principle—evaluate efficacy of an intervention or strategy)
Core elements for implementation of an heat-health action plan
• Establish agreement on a lead organization
• Accurate and timely alert systems (i.e., heat-health warning systems to trigger weather-related warnings, determine the threshold for action, and communicate risks)
• A heat-related health information plan (what to communicate, to whom, and when)
• A reduction in indoor heat exposure (medium- and short-term strategies)
• Particular care for vulnerable population groups
• Preparedness of the health and social care system
• Long-term urban planning
• Real-time surveillance and evaluation

[a]World Health Organization: Europe. Heat-health action plans: guidance. 2008. Copenhagen, Denmark. http://www.euro.who.int/__data/assets/pdf_file/0006/95919/E91347.pdf

currently done? and (2) *Should the temperature indicator thresholds be lowered to account for the HRMM that occurs during less than extreme conditions*? Subsequent considerations highlighted issue related to risk communication and engaging the public. A discussion of these issues follows.

Local-scale population and environmental information (in urban, suburban and rural areas) is required to identify high-risk locations and vulnerable populations and individuals, as well as establish mechanisms to contact those individuals in order for local government agencies (and nongovernmental organizations (NGOs)) to target public health and individual clinical or exposure mitigation interventions and allocate resources to *prevent* HRMM. An example of why local-scale information across the urban-to-rural gradient (i.e., not just urban areas) is necessary lies in the fact that while only 6 % of California's population lives in areas designated as rural, the rural populations tend to be older, with about 20 % of Californians ≥65 years of age living in a rural area [111, 112]. The older adults residing in rural areas tend to be less healthy, with higher rates of overweight/obesity, physical inactivity and food insecurity, and less access to medical resources, than older adults living in suburban areas; for a number of measures, rural older adults are more similar to their urban counterparts than to those in suburban areas [111]. Prior epidemiologic evidence of spatial heterogeneity in HRMM indicates that exposure-response relations derived from one community may not be applicable in another location [27], which combined with differential distribution of vulnerable populations reinforces the need for location-specific data at the finest spatial resolution possible. Community vulnerability mapping, facilitated by the use of geographic information systems (GIS) and advances in geospatial analysis, including methods of protecting

confidentiality of individuals [28] is an important tool to identify at-risk populations, determinants of risk, and evaluate efficacy of interventions through ongoing surveillance.

The need for local-scale information partly informs the answer to the first question. (*Should the definition of a heat wave and heat alert criteria be based on morbidity rather than mortality-response studies*?) In general, administrative morbidity data (e.g., emergency department contacts, hospitalizations) are less readily available (especially for research) and there can be wide variation in quality and content. However, when they are available, the benefits are that there are many more observations representing a broader cross-section of the population, and heat-related morbidity outcomes occur more frequently than deaths, providing significantly larger sample sizes, which usually provides greater spatial coverage and density at finer spatial resolution (e.g., patient residence Zip Code [postal code]). These attributes facilitate evaluation of HRMM risk and vulnerability factors at a fine spatial scale and the provision of local information. There are also good reasons for reliance on mortality as an endpoint. Vital statistics death data are almost always available and are collected with some degree of consistency, their use generally generates less concern with issues of confidentiality, and there are long records across many years lending them to time-series analyses and application of similar heat-mortality modeling strategies in diverse locations. However, use of mortality data has the implicit assumption that deaths represent the most extreme endpoint of a fixed chain of events, i.e., people are exposed to heat, get sick, and then die, and those deaths can (always) be used as a marker of a relevant population exposure and of a predictable risk. Evidence suggests this is not necessarily the case, as mortality may strike quickly prior to the notice of emergency responders and affects elderly, socially isolated, and nonmobile populations [113, 114]. Thus, to the extent the spatial distribution of vulnerable subgroups more likely to die does not track with subgroups who are more likely to contact an emergency department, mortality-based analyses, and heat alert criteria derived from those analyses from one location would not necessarily provide the best information to reduce risk of morbidity or mortality in another location.

An analysis of hospitalizations and emergency department visits (ED) for all-causes and selected causes during the 2006 California heat wave revealed an intriguing and important observation related to spatial variation in different health outcomes [14]. In that analysis, the State was divided into six geographic regions, based approximately on climate zones, each comprised of multiple counties. Risk ratios (RR) that compared rates during the heat wave and during a referent period (each period = 17 days) in the same summer were computed. Unexpectedly, while the highest risk of HRI ED visits (RR = 23.1, 95 % CI: 15.1, 37.1) occurred in the usually cooler region of central coast counties (including San Francisco), there were too few hospitalizations to calculate a risk estimate (due to small cell sizes and required data suppression) for that region (and two other regions). In contrast, in the Central Valley (a much warmer region), the HRI ED-visit risk was substantially lower, but risk of hospitalization for HRI was very high (RR = 17.1, 95 % CI: 9.8, 36.3). That observation is of particular interest because when the

~140 coroner-reported deaths attributed to hyperthermia (126 of the cases were classic heat stroke) during the heat wave were evaluated the majority occurred in the Central Valley, which is a more rural agricultural region and an area with many socioeconomic-driven health disparities [35]. Taken together, the findings indicate the importance of examining/comparing different measures of health impacts—ED, hospitalizations, and deaths—for which the spatial heterogeneity may reflect a variety of determinants of risk that could influence/inform intervention and adaptation strategies. Thus, when possible, heat alert criteria would ideally reflect the composite information.

With respect to the second question, there are practical reasons for continuing to use extreme temperature thresholds (usually the 95th or 99th percentile of daily maximum temperature or temperature-humidity index) to trigger emergency response protocols and to develop supplemental strategies to diminish the health risks associated with usual warm season elevated temperatures. The primary reason being in many locations lower thresholds would be met repeatedly (if not almost continuously), especially during the hottest months. For example, in a Zip Code-level analysis of emergency department visits in California in the warm seasons (May–September) of 2005–2008, significant increases in patients diagnosed with electrolyte imbalance were observed when deviation of the daily maximum temperature from the Zip Code-specific seasonal mean daily maximum temperature was +6 °C (about the 88th percentile for most locations) [28]. Thus, redefining the threshold criteria for issuance of heat alerts based on this relatively low threshold would not likely be the optimum strategy to reduce public health risk. Not only is it impractical and a resource burden to keep the emergency response and public health infrastructures for EHE risk mitigation in a near-constant state of activation, the communities and populations would likely become desensitized to public health messages about the potential health risks of heat exposure and not take requisite precautions even when a severe EHE is forecast.

There must be a careful balance between informing and overwhelming (and desensitizing) the public with information on risk and prevention of HRMM across the full range of ambient heat exposures. This becomes even more of an issue when trying to share information about joint hazards (e.g., heat and air pollution), while also trying to promote health-protective measures such as exercise. Thus, one of the most critical elements of any heat-health action plan, whether aimed at just EHE or also considering less-than-extreme temperatures, is an evidence-based well-designed communication and education-outreach plan (e.g., the heat-related health information plan suggested by WHO). An essential part of the plan is ensuring the public health messages and recommended actions are correct and that they are effective, and if they are not effective, the reasons and how to remedy the deficits. A prime example of an action that could be effective but is not always is the recommendation, usually targeted to older adults or those with chronic health conditions, to use home air conditioning or go to an air-conditioned location such as a “cooling center.” Experience in California and elsewhere indicates cooling centers are often underutilized, including by older adults, which has led some municipalities to consider not opening centers to save the expense of their operation. Among the

recognized ancillary actions required to increase use of centers (cooling or for other emergencies) is to identify persons needing transportation to the center and then provide that service. In addition, emergency plans must consider care of companion animals as many people will not evacuate if they have to leave their pets behind.

It is well established that public health messaging can be a powerful tool for health promotion and protection, and obtaining such information from multiple sources (top-down (e.g., government issued health warnings) and bottom-up (e.g., healthcare provider)) can enhance the public's awareness and adoption of health-protective measures (to improve overall health or in emergencies). However, the implications of the observations about perception of individual risk among vulnerable populations strongly point to the need for innovative approaches and testing the efficacy of those approaches, as well as additional research. That said, the reasons vulnerable populations may not take health-protective measures (even when they are aware of a heat alert and heard public health warnings), such as using a home air conditioner, are complex and may reflect their knowledge, attitudes, and beliefs about the level of personal risk related to their age or chronic illness [115]. For example, as noted by Richard et al. [115], many older adults do not see themselves as old or at risk, and the individuals who believe limitations in their lives are related to aging are less likely to adopt preventive or adaptive behaviors. Socioeconomic deterrents to air conditioning use may be less of a factor than perception of risk [115]. In addition, the source of information about their vulnerability, including from their physicians, may not influence their perception of risk or adoption of protective measures [115]. Direct one-on-one contact and provision of education and assistance is one solution when individuals cannot due to mental or physical limitations, or who do not of their own accord, take preventive measures.

In general, and to enhance the efficacy of direct contacts, there is an urgent need to engage and educate a wider range of stakeholders, especially social service and healthcare providers, and persons in direct contact with vulnerable populations than are currently knowledgeable and proactive about reducing risk of HRMM among the populations with which they interact. In addition to older adults, the chronically ill and socially isolated, this is especially important for reducing risk of HRMM among infants and children. Children's physical and emotional development and their location-time-activity patterns clearly can contribute to differences in ambient heat exposures, exercise-related heat loads, and ultimately to risk of heat stress and HRI. Infants do not have the motor skills to remove blankets or remove themselves from hot environments [51], young children may continue to play outside even when overheating (past their thermal comfort zone) and often do not know/or sense the need to drink fluids [86], and young athletes may push themselves well past thermal comfort levels that are signaling heat stress and illness onset [86]. It thus becomes imperative that adults (parents and other caregivers, teachers, sports coaches, and observers) be cognizant of the risks and remedies and ensure all precautions and necessary actions be implemented to guarantee the safety of children. Specific guidance for each group needs to be built into the heat plan communication and education element.

A key to reducing HRMM is to have a full heat-health action plan with all the elements outlined (Table 6.4); if the requisite resources (including data on where vulnerable individuals/populations reside and the optimum mode for directly contacting them) are not available at the outset, then the plan should include specific contingencies to fill resource gaps, and timelines and steps to build the infrastructure. Unfortunately, even in developed nations EHE emergency response plans are often not available or of inconsistent quality, as was found to be the case in a survey of selected municipal heat wave response plans from cities in the United States that had a history of or were at risk for heat-related mortality [113]. Adding elements to plans to address HRMM that occur at less-than-extreme temperatures will add a layer of complexity; however, with climate-change-related rising temperatures and increased variability superimposed on the existent risks, this is an essential task. Regardless of the apparent completeness of the plan, once developed it will need to be regularly evaluated for its efficacy and updated to reflect lessons learned.

Conclusions

The rapid convergence of all of the climatologic and anthropologic changes in the present and over the very near term (next 2 or 3 decades) and throughout the twenty-first century exceed the current adaptive capacity of many if not most human social systems around the globe to cope with rising temperatures and increasing frequency and magnitudes of EHE. At all levels—from global to local—there needs to be proactive development of a broad range of strategies to reduce the societal, public health, and healthcare burden of HRMM, especially through primary and secondary prevention of chronic and communicable diseases. This will require an integrated multidisciplinary approach to evaluate and define the problem, including the determinants of individual and population vulnerability for HRMM, and develop the solutions in consideration of those vulnerabilities reflecting both morbidity and mortality. The conceptual framework of the Environmental Health Multiple-Determinant Model of Vulnerability provides a tool that allows quantitative and qualitative consideration of factors that independently or jointly confer increased (or diminished) risk of HRMM and identification of strategies to reduce that risk, including those that might not be evident when the problem is viewed less holistically. Furthermore, it fosters multidimensional thinking when developing/applying solutions, including revealing opportunities to integrate climate change mitigation and adaptation strategies that can realize co-benefits for public health and environmental welfare, and/or identify potential adverse unintended consequences of strategies.

Fortunately, through strategic development and implementation of “top-down” and “bottom-up” HRMM risk mitigation policies and actions that are coordinated with and leverage existing global, regional, national, and local public health and healthcare services programs targeting the root causes of poor health, as well as programs aimed at pollution (including GHG) and exposure prevention, significant

progress can be made towards reducing HRMM efficaciously and cost effectively. The global interconnectedness of economies and of the health and welfare of populations creates an imperative for nations to work together to prevent and/or respond to all of those challenges.

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