Heat & Health in vulnerable populations

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Heat & Health
in vulnerable populations

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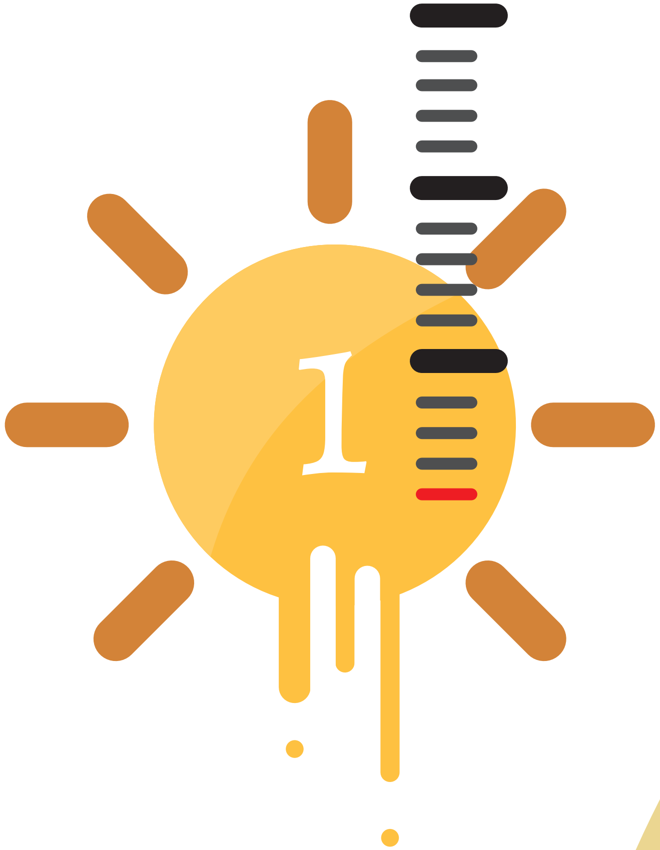


Chapter 1

General introduction and outline of thesis

1.1. CLIMATE CHANGE AND HUMAN HEALTH

Climate change poses a major threat to human health. Since 2017 extreme weather is ranked as the most likely threat for humanity and in 2021 climate action failure is ranked as the second-highest of the most impactful risks facing our society and everyday life of the next decade (1). The average global temperature increased over 1°C in the past 40 years and heat waves are becoming more frequent, more intense and longer lasting (2-4). These heat waves have severe consequences for all populations, but especially for vulnerable people or people directly exposed to the heat while exercising or working. Both morbidity and mortality due to heat increase significantly when ambient temperature rises (5). A recent study showed the attributable mortality to climate change during warm seasons is visible in every continent (6).

There are many factors influencing the vulnerability of humans to heat-related morbidity and mortality, such as environmental parameters, physiological characteristics and human behaviour. All humans experience adverse effects of the heat, but these can be exacerbated or mitigated by adapting behaviour. To which extent behaviour needs to be adapted to limit the adverse effects of the heat depends on physiological characteristics, as humans differ in their susceptibility to the heat. Figure 1 provides an overview of the influence of environmental parameters, physiological characteristics and thermal behaviour on heat strain. In the text below all factors are discussed in more detail, as well as how these factors can be combined in tools to provide warnings and advice regarding heat stress and heat strain to the general public.

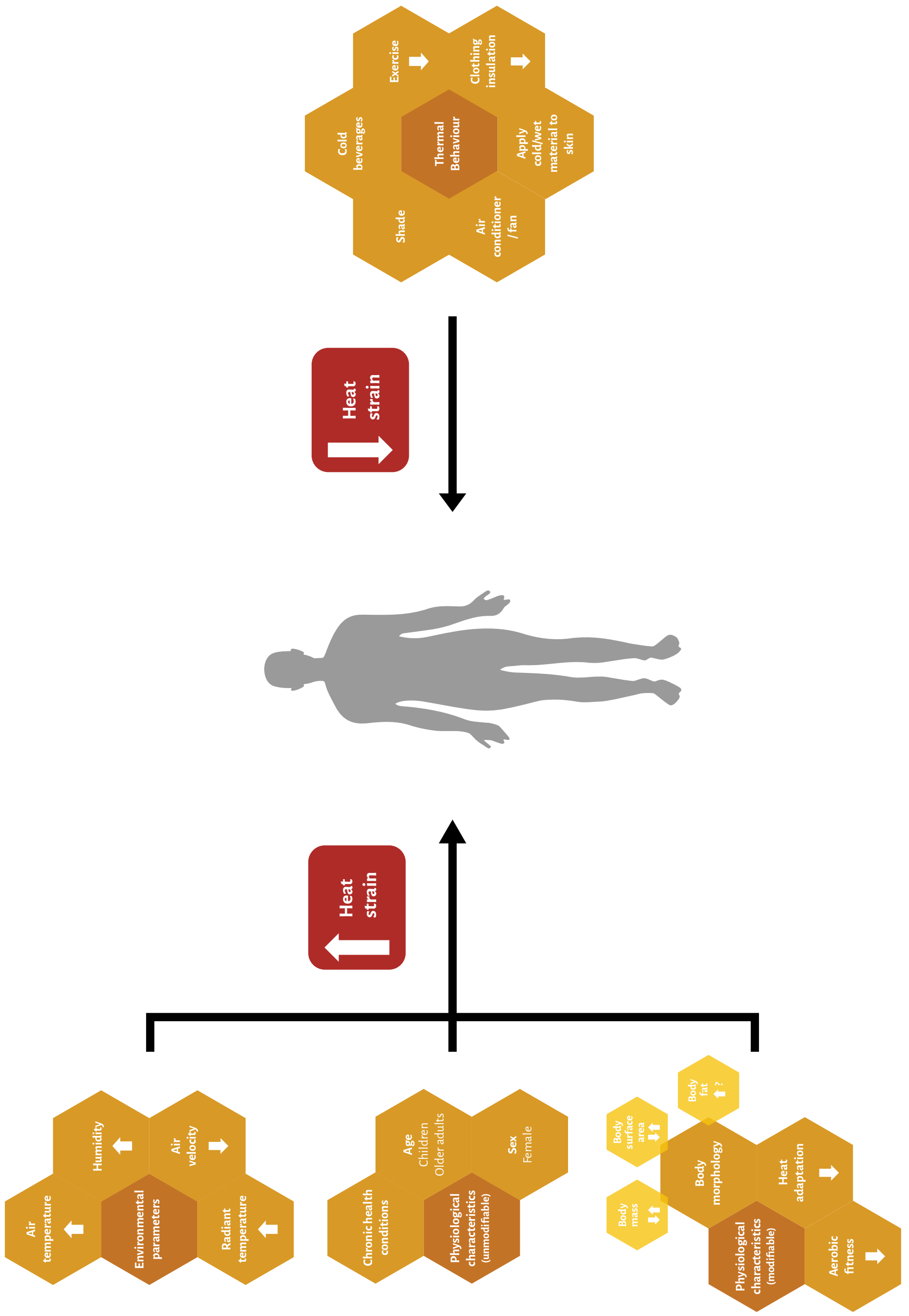


Figure 1. Diagram of the influence of environmental parameters, physiological characteristics and thermal behaviour on heat strain

1.2. ENVIRONMENTAL PARAMETERS

Environmental parameters influencing heat strain are air temperature, humidity, air velocity and mean radiant temperature (7). Air temperature is the temperature of the air that surrounds the human body and is the driver for the dry heat exchange between the air and the human body (7). Humidity is distinguished into absolute and relative humidity: Absolute humidity is the water vapor, in grams of moisture per cubic meter of air (g m^{-3}), regardless of temperature, and relative humidity is the amount of water vapour present in air expressed as a percentage of the amount needed for saturation at the same temperature (8). The vapor pressure gradient between the environment and the skin influences the amount of sweat that can be evaporated, as sweat can only be evaporated if the water vapor pressure on the skin is higher than in the surrounding environment (7, 9). The air velocity influences the dry heat loss and the amount of sweat that can be evaporated from the skin by the speed the air moves across the human body (7, 10). Mean radiant temperature is the energy transmitted by electromagnetic waves and is defined as: 'The temperature of a uniform enclosure with which a small black sphere at the test point would have the same radiation exchange as it does with the real environment' (7, 8). The sun is the main source of radiation outdoor (7, 8).

These four environmental parameters are often combined into a thermal model or index to give an indication of the thermal environment an individual is exposed to. More than one hundred heat stress models or indices have been developed over the last decades to quantify heat stress and/or heat strain (11, 12). Heat stress is defined as "a change in the thermal relation between a temperature regulator (e.g. human) and its environment which, if uncompensated by temperature regulation, would lead to hyperthermia (13). Heat strain is defined as "Any deviation of body temperature induced by sustained heat stress that cannot be fully compensated by temperature regulation" (13). A frequently used heat stress index and heat strain model are the Wet Bulb Globe Temperature (WBGT) and the Predicted Heat Strain (PHS) (explained below in detail). Both the WBGT and PHS have advantages and limitations. The advantages of the WBGT are that it is an internationally accepted heat stress index and therefore widely used, simple to interpret and can be derived from widely available weather data (14). However, specific and often expensive measuring instruments are needed, or algorithms have to be used to calculate WBGT from weather data. And in some cases, the used exposure limits are not applicable to all climates (15). PHS on the other hand, can be applied in all climates to calculate changes in core temperature and water loss, which is then used to estimate the physiological strain and maximum exposure time based on certain criteria. A limitation of the PHS is that a direct reading instrument is not available. Typically, it is calculated using a computer program therefore there is no instantaneous result, limiting its usability in the field (15). Furthermore, information needed for input (weather data, activity, clothing, etc.) needs to be very accurate otherwise the calculated heat strain is unreliable.

1.2.1. Wet Bulb Globe Temperature (WBGT)

The WBGT is a heat stress index and its value gives an indication of the thermal environment an individual is exposed to (16). The WBGT can be calculated for outdoor situations using equation 1. T_{nw} represents the natural wet bulb temperature, which is the temperature measured by a sensor covered with a wetted wick, unshaded and not protected from prevailing wind (16). T_g represents the globe temperature, which is the temperature measured by a sensor placed in a black bulb and T_a is the air temperature (16). In an indoor situation T_a is similar to T_g and can be calculated with equation 2.

$$WBGT_{outdoor} = 0.7T_{nw} + 0.2T_g + 0.1T_a \qquad \textbf{Eq. 1}$$

$$WBGT_{indoor} = 0.7T_{nw} + 0.3T_g \qquad \textbf{Eq.2}$$

In ISO 7243 reference values are provided to represent the thermal environment in which individuals are in compensable heat stress, which means the body should be able to maintain thermal balance (16, 17). Individual factors that are taken into account for the WBGT reference values are metabolic rate, acclimatization status and clothing. If WBGT exceeds the reference value it is advised to reduce the heat stress or carry out a detailed analysis of the experienced heat stress by the PHS described in ISO 7933 (16).

1.2.2. Predicted Heat Strain (PHS)

The PHS is a thermal model which uses the thermal balance equation (Eq. 3) to calculate the maximal exposure time to a thermal environment based on core temperature and dehydration (18). The part of equation 3 before the equal sign, M – W, represents the heat production in the body where M is the metabolic rate and W the effective mechanical power. The part of equation 3 after the equal sign, $C_{res} + E_{res} + K + C + R + E$, represents the heat exchange of the human body with C_{res} and E_{res} the convection and evaporation of the respiratory tract, and K, C, R and E the conduction, convection, radiation and evaporation, respectively, of the skin. S represent the heat storage in the body (18).

$$M - W = C_{res} + E_{res} + K + C + R + E + S \qquad \textbf{Eq.3}$$

In ISO 7933, the maximal exposure time is reached when core temperature exceeds 38°C or when a certain percentage of body weight is lost by sweating. For situations where an individual can drink freely, the maximal sweat loss is set on 7.5% of the initial body weight for the average population and on 5% to protect 95% of the working population.

When an individual cannot drink the maximal sweat loss is set on 3% (18). Individual factors that are used to calculate the maximal exposure time are metabolic rate, acclimatization status, clothing, body composition and access to fluids.

1.3. PHYSIOLOGICAL CHARACTERISTICS

The level of vulnerability to heat depends on many individual physiological characteristics. In this section the main factors for this thesis are discussed. A recent review of Foster et al. (2020) (19) ranked the impact of the individual factors on the heat stress response. Body mass and heat adaptation were ranked as high impact; aerobic fitness, age, sex and chronic health conditions as moderate impact and body fat and skin surface area to body mass ratio as low impact (19). A distinction can be made between individual factors which can be modified, such as body morphology (with height as an exception), heat adaptation status and aerobic fitness, and individual factors that cannot be modified, such as age, sex and chronic health conditions (figure 1).

1.3.1. Modifiable individual factors

1.3.1.1. Body morphology

Body morphology has a strong impact on the heat stress response of the human body (19-21). Body mass of an individual acts as a heat sink, which means more heat can be stored with a higher body mass (20, 22). On the other hand, exercise costs more energy in individuals with a higher body mass, resulting in a larger heat production (21). During work at a fixed metabolic rate a higher body mass is considered to be an advantage while working in the heat, as core temperature remains lower (19, 20, 23).

Body surface area, especially relative to mass, affects the whole-body heat exchange, as a larger body surface area results in greater absolute values of convection, radiation and evaporation (21). Therefore, more heat is lost in an individual with a larger body surface area as long as the air temperature is lower than the skin temperature. On the other hand, more heat is gained via the skin if the air temperature is higher than the skin temperature.

Adipose tissue has a lower heat capacity than lean tissues (21). Therefore, it is expected that individuals with more adipose tissue have a greater change in core temperature under similar conditions compared to their counterparts with less adipose tissue. However, many studies aiming to study the role of body fat in thermoregulation lack control for confounding factors such as metabolic heat production and body mass (24). One study showed significant differences in core temperature between groups of really low and high adiposity (>20% difference between groups) (25), while this was not found in other studies with smaller differences on body fat percentage (<10% difference between groups) (21, 23, 26, 27).

1.3.1.2. Heat adaptation

The human body physically adapts to the heat when the exposure is sufficient and recurrent (28). Most of the adaptations occur in the first four to seven days of heat exposure and include changes in sweat rate, core temperature, heart rate and plasma volume (28). Optimal heat acclimation within a week can be reached by daily exposure to dry heat while exercising for 100 minutes (28, 29). Adaptions occur as well during seasonal exposure, but the extent depends on environmental characteristics, exposure, duration and intensity of physical activity in the heat (30). Previous research has shown that most cases of heat illness occur in the initial days of heat exposure (31), which potentially can be partly explained by a lack of heat acclimatization.

1.3.1.3. Aerobic fitness

Aerobic fitness influences the capability to adjust the heat dissipation of the human body, most likely by affecting the upper limit for heat dissipation (19, 26, 32-35). Exercise training results in cardiovascular and sweating adaptations beneficial for thermoregulation (19). These adaptations due to physical exercise are partly explained by an increased heat acclimation state due to the repeated thermal load put on the human body during exercise (35). Cardiovascular adaptations are, amongst others, an increase in cardiac output and blood volume, resulting in a larger heat transfer via the blood to the environment while exercising in the heat (10). Furthermore, sweat rate at a given percentage of the maximal oxygen consumption (VO_{2max}) is higher in physically fit individuals, increasing the wet heat loss in these individuals (36-38). Therefore, provided hydration is maintained, an individual with low physical fitness is more vulnerable to the heat. Increasing aerobic fitness is named as one of the most effective solutions to reduce heat strain in manual labourers often exposed to high temperatures (34).

1.3.2. Unmodifiable individual factors

1.3.2.1. Age

A higher morbidity and mortality in the heat is observed in both children, especially the youngest (< 5 years), and older adults (39-41). Children differ from adults in their morphology, in the regulation of cutaneous vasodilatation and sweating, and in their mechanical efficiency (42). Children have, for example, a greater body surface-area-to mass ratio than adults, meaning in an environment where ambient temperature is lower than skin temperature, children would dissipate more heat per unit body mass than adults. However, children would gain more heat if ambient temperature is higher than skin temperature (41, 43).

Furthermore, the vasodilatory response in children appears to be greater than in adults, resulting in a higher dry heat loss when the ambient temperature in lower than skin temperature (42, 44, 45). In environments where ambient temperature exceeds skin temperature and dry heat loss is no longer effective, heat loss must occur through evaporation to maintain thermal balance. Whilst all sweat glands are developed by the age of three years, it is not until puberty that the sweat glands are fully grown and matured. Therefore, pre-pubescent children have a lower output per sweat gland (46). The lower sweat output does not necessarily mean children are less effective sweaters, as studies suggest children have a higher sweating efficiency due to smaller and concentrated sweat drops (47, 48).

Beside differences in heat loss, there are also differences in metabolic heat production. Children produce more heat per unit body mass during exercise, as they consume more oxygen during exercise (42, 49, 50). At a certain walking or running speed children have to take more strides than adults due to their shorter legs, resulting in a higher heat production per unit size (46, 51-53).

Heat-related mortality is reported to be highest amongst older adults (54, 55). In general older adults are considered to be over 65 years (56), but the decline in thermoregulatory function occurs progressively. A study showed that after the age of 20, whole-body maximum heat loss decreases with 4% every decade (57). The reduction in the ability to lose heat with aging is for the largest part explained by the lower overall sweat rate in older adults, as evaporative heat loss is the strongest avenue of heat loss of the human body in the heat (55, 58). In older adults the onset of sweating is delayed and the output per sweat gland is reduced, but the number of activated sweat glands remains the same (59). Furthermore, skin blood flow adjustments to heat appears to be reduced in older adults as well. On average, the increase in skin blood flow is 25 to 50% lower in healthy older adults while exercising in the heat compared to their younger healthy counterparts, mainly because the sensitivity of the vasodilator system for, amongst others, co-transmitters is reduced (59). Another cause for compromised thermal tolerance in older adults is the reduced redistribution of blood from the renal and splanchnic system to the skin (59). As a result from the reduced sweat output and the reduced skin blood flow less heat is dissipated to the environment and heat storage in the body is higher (60). Furthermore, an attenuated cardiac output and reduced thirst stimulus leading to an often chronic status of dehydration in older adults plays a role in the reduced skin blood flow with aging as well (55, 59). Cardiac output is reported to be lower in older adults during passive heating (55), however results from studies investigating the differences in cardiac output between older and younger adults while exercising in the heat are not unambiguous (59).

Aerobic fitness plays a major role in the significance of the decline of the thermoregulatory system with aging. Many studies suggest there are no or only small differences in the ability to dissipate heat between older and younger adults when matched for aerobic fitness (55, 59). Aerobic exercise training improves sweating responses (35), cardiac output and skin blood flow at all ages. These physiological adaptations due to aerobic exercise training are most likely a result of increased aerobic fitness combined with an increased heat acclimation state, as exercise puts repeated thermal stress on the human body (61, 62). However, for older adults it is more difficult to remain physically fit and it is unclear to which extent VO_{2max} can be maintained with ageing (59).

1.3.2.2. Sex

Sex differences in thermoregulation exist due to differences in anthropometrics, hormones and aerobic fitness (62, 63). In general, women have a lower body mass, a higher body fat mass and a larger surface area-to-mass ratio (62). The lower body mass of typical women results in greater and quicker increases in core temperature while exercising on the same absolute intensity as men (21, 64, 65). In addition, adipose tissue has a lower heat storage capacity than lean tissues, therefore greater changes in core temperature are expected in people with more body fat at a certain change in body heat content and mass (21). However, as long as air temperature is lower than skin temperature, the larger surface area-to-mass ratio of most women results in faster heat loss (62). When air temperature is higher than skin temperature the larger surface area-to-mass ratio of women results in faster heat gain (62). .

Furthermore, women have in general a lower aerobic fitness than men (66, 67). Therefore, women are often at a higher percentage of their maximal aerobic capacity when exercising at a fixed intensity compared to men. Conversely, when working at the same relative exercise intensity women are typically working at a lower absolute intensity, and therefore a lower metabolic heat production, compared to men (68).

Sweat capacity is lower in women, even when controlled for physical traits and metabolic rate, but mainly when the requirements for sweating are near maximum (62, 63). Most likely the difference in sweat capacity is due to a lower maximum sweat gland output in women (19, 69). However, differences in sweat output seem no longer present after heat acclimation (19, 70).

1.3.2.3. Chronic health conditions

Chronic health conditions often accompany ageing and conditions such as cardiovascular and respiratory diseases can have a profound effect on the body's ability to respond to heat stress (19, 54). Cardiovascular diseases are conditions to the heart and circulatory system which compromise skin blood flow or a normal cardiovascular function. During heat stress the heart needs to work harder due to an elevated blood flow to the skin, which can increase the risk of a cardiovascular event in people with cardiovascular diseases (54, 71). Cardiovascular diseases are reported to be one of the main causes of heat-related mortality (72). Another major cause for heat-related mortality are respiratory diseases (72). The thermoregulatory response of the human body to the heat, e.g. the increase in pulmonary ventilation, puts significant stress on the respiratory system (73, 74). Asthma, COPD and bronchiectasis are respiratory diseases which, amongst others, cause an increased morbidity already in moderate heat (75). Individuals with cardiovascular or respiratory diseases are therefore significantly more vulnerable in the heat than their healthy counterparts.

1.4. HUMAN BEHAVIOUR

Human behaviour has a major impact on the severity of the experienced heat strain and is often considered to be the first defence mechanism to keep thermal balance (76). There are many ways people can adapt their behaviour to limit heat strain. For example, people can limit their physical activity, reduce the clothing insulation or apply cold and/or wet material to the skin (76-79). Physical activity is a major contributor to the experienced heat strain as the majority of the oxidation of substrates is converted into heat during exercise (80). People can also adapt their surroundings by, for example, the use of an air conditioner or a fan, closing windows during the day or protecting themselves from solar radiation (78, 81).

Not everyone uses these precautionary measures to the same extent (82). It has been reported that older adults are less willing to use adaptive cooling methods, potentially due to reduced sensitivity to thermal comfort, lack of social support or not wanting to be perceived as ‘old’ and ‘vulnerable’ (83). Furthermore, young children are not able to use precautionary measures as they cannot take care of themselves and depend on their parents or caregivers to provide them with a safe environment, clothes, food and water (41, 49, 84). Also, once children can walk they generally engage in more physical vigorous and outdoor activities, which exposes them to more heat stress and heat strain (41, 85, 86). There are sex differences in heat related behaviour as well (62, 82). It has been reported that women are more likely to look for information about the health risks of heat and tend to follow heat protection recommendations better than men (82).

1.5. TOOLS FOR ADVICE REGARDING THERMAL STRESS AND THERMAL STRAIN

Human behaviour is essential to maintain our thermal integrity, but sometimes behaviour is driven by inadequate information and false believes. Information about environmental parameters and individual physiological characteristics combined with thermal models and indices, such as the WBGT and PHS, can be used to warn and advise people regarding thermal stress and thermal strain. Tools, such as mobile applications, can be used to provide this scientifically substantiated information in a user-friendly and broadly understandable manner to the general public. These tools can be used by outdoor workers, (care providers of) children and older adults, athletes or other individuals exposed to the heat for receiving warnings about the current and expected thermal stress and thermal strain, and advice regarding precautionary measures to reduce the adverse effects of the cold or heat.

1.6. OUTLINE THESIS

As described above, environmental parameters, physiological characteristics and human behaviour all influence the vulnerability of humans to heat-related morbidity and mortality. As heat stress is expected to rise due to climate change, tools such as mobile applications may be useful to adjust behaviour based on the knowledge of human physiology. Therefore, the aim of the current thesis was to extend our knowledge on two physiological characteristics influencing the vulnerability of humans in the heat, namely age and sex, as well as how combining environmental parameters with thermal models and indices and individual physiological characteristics can provide individualized advice regarding heat stress and heat strain prevention. The older population is growing rapidly and with the rising temperatures there is an urgent need for more research to reduce the vulnerability of the aged population in the heat. Next, children, elderly and women are much less researched than male adults, and more research regarding age and sex differences is needed for individually focused advice to reduce heat stress and heat strain. In the following chapters new scientific studies on these topics are presented.

As previously mentioned, young children seem vulnerable to the heat due to an undeveloped thermoregulatory system and behavioural dependability. In day-care centres the care providers are responsible for the wellbeing of the children, therefore in *Chapter 2* the ability of care providers in day-care centres to estimate the thermal state of young children and their knowledge on this topic was investigated.

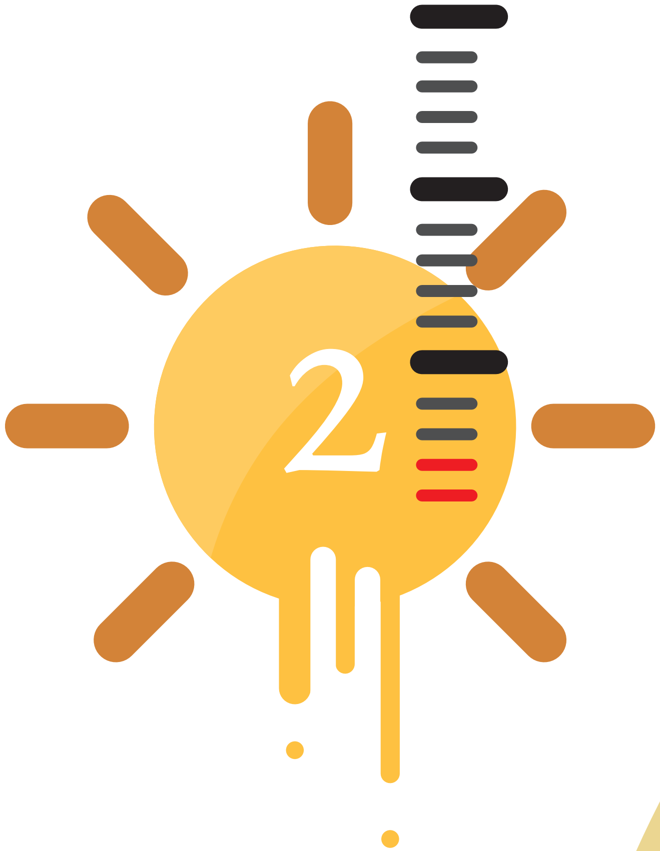
Despite the scientific evidence indicating sex differences in thermoregulation, in ISO7243 no distinction is made for this in the critical WBGT, which are the environmental thresholds above which heat gain exceeds heat loss and body core temperature rises. In *Chapter 3* the results are presented of a study investigating the critical WBGT for men and women in rest and low-to-moderate intensity exercise.

Increased mortality in the aged population at low and high temperatures are repeatedly reported, but sex differences in temperature-related mortality are equivocal. In *Chapter 4* we assessed sex differences in temperature-related mortality for the Netherlands.

Rising and more extreme temperatures due to climate change already occur and are expected to become more severe, longer lasting and more frequent in the coming years, putting severe stress on the human body. However, humans may be resilient and in *Chapter 5* we investigated the extent to which humans are able to adapt to the increasing temperatures due to climate change by a shift in the minimum mortality temperature, which is the mean daily temperature at which the lowest mortality occurs.

Mobile applications combining thermal models and indices with environmental parameters and individual physiological characteristics may be beneficial for providing advice regarding thermal stress prevention to the general public. In *Chapter 6* the validation of such a tool, ClimApp, is reported.

Chapter 7 presents a summarising discussion of the main findings of the scientific papers presented in this thesis.



Chapter 2

Care provider assessment of thermal state of children in day-care centres

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2.1. ABSTRACT

Young children are vulnerable to extreme temperatures due to their physiological and anatomical characteristics and behavioural dependability. The latter is a relatively unexplored area. Therefore, the current study investigated the skin temperature as a proxy of the thermal state of children and care providers in day-care centers, the ability of the care providers to estimate the thermal state of the children and their knowledge on this topic. Results from 104 children (< four years old) and 58 care providers recruited from six different day-care centers in winter and summer in the Netherlands show that there was no difference in thermal state between the children and care providers. A significant relation ($p<0.05$) was found between skin temperature of the care providers and thermal sensation in winter and summer, but not for the skin temperature of the children and the assessed thermal sensation score of the children by the care providers ($p>0.05$). Furthermore, many care providers had difficulties naming symptoms of heat illness and the care providers with ≤5 years work experience had a lower knowledge level of thermoregulation than care providers with >5 years work experience. It is recommended to train care providers in thermal assessment, in particular novice care providers that have less knowledge on this topic.

2.2. INTRODUCTION

The ability of children to cope with extreme temperatures is limited compared to adults, mostly due to physiological and anatomical characteristics (41, 87-89). For instance, since the sweat glands of children are not fully developed until after puberty, children have lower sweat rates and increased risk of thermal injury in the heat (46, 90). In addition, children have a larger body surface area-to-mass ratio in comparison to adults, which can lead to a faster and greater change of body temperature in an environment with extreme temperatures (41). Moreover, metabolic rate is higher due to low mechanical efficiency (87). Consequently, physical activity at the same intensity results in a greater heat production in children compared to adults (46, 52).

Besides thermoregulatory differences between children and adults, behavioural dependability is another characteristic that results in enhanced vulnerability in the youngest (< four years old) children. Children of this age group depend on their parents or care providers to get dressed and may have difficulties expressing discomfort regarding temperature sensation or thirst (49, 84). Furthermore, children generally engage in more physical activities outdoors than adults (41). Previous research has shown that significantly more children were brought into the emergency department during days with high ambient temperatures compared to days with lower ambient temperatures (91). To reduce these risks, parents and care providers should be well informed about the effect of the environmental conditions on children's health and wellbeing and what precautionary measures are appropriate, as this most likely avoids morbidity and mortality in children due to the heat (88). Knowledge about this is even more relevant since more extreme weather events, like heat waves, occur due to climate change (92).

In the last few years, the number of children below the age of four attending a day-care centre has increased significantly in the Netherlands. In the first quarter of 2019, 338,000 children went to a day-care centre at least one day a week, which resulted in 88,000 more children than in 2015 (93). Care providers are responsible for the wellbeing of these children in these day-care centres and with the rise in attendance and the increased prevalence of extreme weather conditions, it is imperative that these care providers are well informed about the thermoregulation of children, potential temperature related risks and how to act in the event of a temperature related illness. In particular, if a child has symptoms of heat illness immediate action is required (94). However, to the authors' knowledge, there are no studies investigating thermal stress in children in day-care centres or studies that have examined the knowledge of the care providers on this topic. The buildings of day-care centres in the Netherlands are often old and the quality of the indoor climate is insufficient (95). Whilst a few studies have investigated the effect of indoor air quality, including temperature, on respiratory health of the children in day-care centres (96-100), these studies did not perform any physiological measurements. This study therefore investigated the effect of ambient temperature on the thermal state of children in day-care centres in summer and winter in the Netherlands. Thermal state in this study is defined by the mean skin temperature (T_{sk}) of four different body locations, since previous studies have shown that T_{sk} is a good predictor of thermal sensation (101, 102). The ability of the care providers to estimate the thermal state of the children was examined, as well as the knowledge of the care providers about thermoregulation in children, temperature related illnesses and precautionary measures to reduce cold and heat exposure. It is hypothesized that the thermal state of the children is different than the thermal state of the care providers due to the difference in thermoregulation and surface to volume ratio, as well as differences in behaviour during the day. Further, it is hypothesized that care providers cannot correctly estimate thermal state of the children for care providers if the thermal state is different, but that due to sufficient knowledge and experience appropriate actions are taken within day-care centres.

2.3. METHODS

2.3.1. Ethical approval

The current study was approved by the ethical committee of the Faculty of Behavioural and Movement Sciences of the Vrije Universiteit Amsterdam in the Netherlands (VCWE-2017-183). Informed consents were conducted according to the declaration of Helsinki and signed by the parents of the children to approve participation of their child, as well as by the care providers to approve their own participation.

2.3.2. Participants

Children and care providers were recruited from six participating day-care centres across the Netherlands (Arnhem, Assen, Emmen, Amsterdam, Zuidhorn and Groningen). Care providers are defined in this study as the day-care employees responsible for the wellbeing of the child during the time the children are present in the day-care centre. Children were included if their parents approved their participation. Furthermore, both children and care providers were excluded if they had a fever or another illness influencing body temperature. Parents indicated at arrival if their child had a temperature or fever, but usually the child was not in the day-care centre in case of being ill. The care providers mentioned themselves if they felt ill or they were not in the day-care centre as well.

2.3.3. Measures

At each day-care centre measurements took place one day in winter and one day in summer in the year 2018 and 2019. Both days the same measurements were completed three times a day; in the morning (9.00-10.00 am), midday (12.00-13.00 pm) and in late afternoon (15.00-16.00 pm).

To assess the out- and indoor climate of the day-care centres the temperature, humidity and Wet Bulb Globe Temperature (WBGT) was measured (3M™ QUESTemp°, St. Paul Minnesota, USA, accuracy temperature 0.5°C, relative humidity 5%). T_{sk} of the ring finger, forearm, cheek and forehead of the children and care providers were measured with a Voltcraft IR-230 infrared thermometer (Conrad Electronic, Hirschau, Germany, emissivity 0.95). These locations were chosen as they are not covered by clothes (only the forearm on a few occasions) and for ease of access. The sensor was positioned 3 cm from the skin without direct skin contact. Three devices were used. Although the accuracy of the devices was specified at 2.5°C for the range of -35 to 250°C, a comparison using an iButton (DS1922L, Maxim Integrated Products Inc, Sunnyvale, CA, USA) for the expected temperature range of T_{sk} (between 17°C and 37°C) resulted in a deviation of 0.3 ± 0.5°C (mean ± SD).

Whole body thermal sensation (TS) was assessed with a 9-point scale (from -4 = very cold to +4=very hot) (103). The care providers scored their own thermal sensation (TS_{cp}) and were instructed to report the TS that they believed matched best with that of the child (TS_{child}). Physical activity of the children who were able to walk was determined with a pedometer (Yamax SW200, Tokyo, Japan, accuracy 10%). Pedometers are proven to be a reliable measure of physical activity, also in pre-school children (104, 105). The children wore the pedometer from the moment they arrived until they, or the researcher left. The clothing of the children and care providers were assessed and afterwards the thermal insulation of the clothing was calculated in clo (1 clo = 0.155 m2·K·W-1) using ISO standard 9920 (106). The weight and height of the children was measured with a weighing scale (Medisana, Germany, Neuss) and measuring tape.

The care providers knowledge of thermoregulation in children, temperature related illnesses and precautionary measures to reduce cold and heat exposure were assessed with an interview containing eight open ended questions specifically developed for this study (see Appendix A for the questions translated from Dutch to English). The interviews with the care providers were analysed by two independent researchers (authors MF and MZ) by quantifying each answer into a category. Next, scores were defined for the questions regarding the knowledge of the care providers what is insufficient and sufficient knowledge (see Appendix B for the classification of the knowledge scores).

2.3.4. Statistical analysis

The data was analysed using RStudio 1.1.463 and Stata 16.0. Mean T_{sk} was calculated per individual and measurement moment using an unweighted average of T_{sk} of the four locations and was assumed to represent the thermal state of the children and care providers. Analysis of winter and summer data were conducted separately and then combined, with the latter referred to as the 'total period'. To test for differences between the thermal state of the children and care providers at different indoor WBGT temperatures an ANCOVA was performed with T_{sk} of the four locations and mean T_{sk} as a dependent variable, individual (child or care provider) as independent variable and WBGT indoor as a covariate.

Multilevel mixed-effects linear regression analysis was used for part of the analysis as the data is hierarchically structured. Four different models were fitted with each different level (considered levels were day-care centre, group, child and/or care provider) and the residuals were distributed normally. The first model (A) was fitted with a random intercept for child (level 1) and day-care centre (level 2) to test which parameters effect mean T_{sk} of the children the most. Parameters included in this model are in- and outdoor WBGT, clo value, number of steps, BMI, age and sex of the child. The second model (B) was fitted with a random intercept for care provider (level 1) and day-care centre (level 2) to test which parameters predominately affected the care providers mean T_{sk}. Parameters included were in- and outdoor WBGT and clo value. The third and fourth model were fitted with a random intercept for care provider only, to determine the relation between TS_{cp} and mean T_{sk} of the care provider (model C) and between the TS_{child} and the mean T_{sk} of the child (model D).

2.4. RESULTS

In total, 104 children (< four years old) and 58 care providers participated in the current study. Twenty-two children and 16 care providers participated both in winter and summer. Of the 104 children 49 were female and 55 were male. The care providers were all female, apart from one male. Table 1 shows the characteristics of the day-care centres, the children and care providers, separated for winter and summer measurements.

Table 2 shows the mean daily ambient temperature, relative humidity and WBGT measured in the morning, midday and afternoon both in- and outside the day-care centres in winter and summer, as well as the median T_{sk} and clo value of the children and care providers. The median number of steps taken per hour by the children is reported as well. As expected, ambient temperature and WBGT for both in- and outside of the day-care centre were higher in summer than in winter, but no extreme temperatures were observed. Figure 1 shows the relation between indoor WBGT and T_{sk} of the ring finger, forearm, cheek, forehead and the mean of the children and care providers and the results of the ANCOVA are shown in table 3. When considering the total period, significant differences ($P<0.05$) in T_{sk} between children and care providers were found for all four body locations, but not for the mean T_{sk}. Ring finger and forehead of the children was consistently higher, while the temperature of the forearm and cheek of the children was consistently lower than the care providers. In summer and winter separately, the differences in the T_{sk} of the ring finger and forehead were not significantly different between children and care providers, with $p=0.296$ and $p=0.134$ for the ring finger and $p=0.124$ and $p=0.075$ for the forehead in summer and winter respectively.

Table 4 shows the results of the multilevel mixed-effects linear regression analysis for model A, B, C and D for the total period and for winter and summer separately. Mean T_{sk} is mostly dependent on WBGT indoors in both the children ($p<0.001$) and the care providers ($p<0.01$). However, in the winter mean T_{sk} of the care providers is not significantly correlated with WBGT indoors ($p=0.20$), but significantly related to WBGT outdoors ($P<0.05$). Furthermore, mean T_{sk} of the children in the total period is also significantly correlated with physical activity, age and sex ($p<0.05$) and in the summer and the winter separately with the sex of the child ($p<0.05$). No significant correlations are found between the mean T_{sk} of the children and the clothing and BMI and between the mean T_{sk} of the care providers and clothing.

For the total period a significant relation was found between TS_{cp} and the mean T_{sk} of the care provider ($p<0.01$), as well as for TS_{child} and the mean T_{sk} of the children ($p<0.05$). However, when considering summer and winter separately, only a significant relation was found between TS_{cp} and the mean T_{sk} of the care provider ($p<0.01$), and no significant relation was found between the TS_{child} and the mean T_{sk} of the children. Figure 2 shows TS_{cp} and TS_{child} compared to the mean T_{sk} for the total period and winter and summer separately. The boxplot in winter and summer shows a larger variation of mean T_{sk} of the children for most of the TS_{child} compared to the mean T_{sk} and TS_{cp}, which may explain the non-significant relation.

Table 1. Characteristics of the day-care centres, children and care providers during winter and summer

Season	Day-care	Location	Children					Care providers		
			N	Age (Month) (median (IQR))	Gender (M/F)	Height (cm) (median (IQR))	Weight (kg) (median (IQR))	N	Gender (M/F)	Experience (Years) (median (IQR))
Winter	1	Arnhem	10	28 (23 - 32)	5/5	88 (88 - 88)	14 (12 - 14)	8	0/8	12 (4 - 14)
	2	Assen	16	25 (19 - 38)	12/4	88 (81 - 96)	13 (12 - 15)	14	0/14	3 (2 - 5)
	3	Emmen	6	20 (16 - 34)	1/5	82 (80 - 92)	12 (11 - 16)	4	0/4	2 (1 - 7)
	4	Amsterdam	13	23 (17 - 33)	8/5	87 (76 - 97)	14 (10 - 17)	6	0/6	13 (8 - 25)
	5	Zuidhorn	14	27 (18 - 33)	7/7	91 (89 - 100)	15 (14 - 16)	5	0/5	2 (1 - 14)
	6	Groningen	12	24 (20 - 33)	7/5	88 (81 - 96)	13 (11 - 16)	9	1/8	16 (11 - 18)
	All	-	71	26 (18 - 34)	40/31	88 (81 - 97)	14 (12 - 16)	46	1/45	5 (2 - 14)
Summer	1	Arnhem	8	33 (30 - 35)	4/4	93 (91 - 98)	14 (13 - 16)	4	0/4	3 (2 - 8)
	2	Assen	16	23 (21 - 34)	11/5	87 (85 - 95)	13 (11 - 14)	6	0/6	3 (3 - 5)
	3	Emmen	8	30 (20 - 40)	4/4	91 (87 - 98)	13 (11 - 14)	3	0/3	20 (10 - 24)
	4	Amsterdam	10	21 (12 - 29)	4/6	79 (72 - 89)	11 (10 - 13)	6	0/6	13 (8 - 25)
	5	Zuidhorn	5	18 (7 - 27)	3/2	86 (70 - 96)	12 (8 - 13)	2	0/2	7 (4 - 9)
	6	Groningen	8	24 (20 - 35)	2/6	86 (85 - 95)	13 (13 - 14)	7	1/6	17 (12 - 18)
	All	-	55	24 (18 - 34)	28/27	88 (83 - 96)	13 (11 - 14)	28	1/27	10 (3 - 18)

IQR=Interquartile range

Table 2. Median and interquartile range (IQR) of indoor and outdoor temperature (T) (°C), humidity (RH) (%), Wet Bulb Globe Temperature (WBGT) (°C), and mean skin temperature (T_{sk}) and clo (median (IQR)) of the children and care providers in winter and summer averaged over all included day-care centres for time of day (morning, midday and afternoon). The median number of steps per hour taken in winter and summer by the children is reported as well.

Season	Time of day	Outdoor			Indoor			Children			Care providers	
		T (°C) (median (IQR))	RH (%) (median (IQR))	WBGT (°C) (median (IQR))	T (°C) (median (IQR))	RH (%) (median (IQR))	WBGT (°C) (median (IQR))	T_{sk} (°C) (median (IQR))	Clo (median (IQR))	Steps (median (IQR))	T_{sk} (°C) (median (IQR))	Clo (median (IQR))
Winter	Morning	6.0 (5.6-7.5)	62 (44-67)	5.8 (4.7-7.0)	20.2 (19.1-21.1)	43 (37-51)	16.6 (15.8-17.4)	29.5 (27.3-31.1)	0.7 (0.6-0.8)	756 (554-921)	29.6 (27.6-30.6)	0.8 (0.6-0.8)
	Midday	7.2 (6.3-10.6)	50 (48-60)	6.7 (5.5-9.0)	20.6 (19.5-21.4)	44 (34-50)	17.1 (16.1-18.1)	30.1 (28.1-31.5)	0.7 (0.6-0.8)	-	30.4 (28.9-31.5)	0.8 (0.6-0.8)
	Afternoon	9.4 (7.6-11.7)	48 (41-65)	6.7 (0.3-9.1)	20.3 (19.6-22.0)	41 (32-49)	16.9 (16.2-17.9)	29.7 (28.3-31.7)	0.7 (0.6-0.8)	-	30.4 (29.6-31.7)	0.8 (0.6-0.8)
Summer	Morning	20.3 (18.4-20.6)	66 (51-69)	18.6 (17.7-20.2)	22.2 (21.3-23.4)	61 (57-67)	19.7 (19.4-20.9)	30.9 (29.8-31.9)	0.5 (0.4-0.8)	742 (592-933)	30.9 (30.2-31.6)	0.5 (0.5-0.6)
	Midday	21.5 (20.4-22.8)	49 (44-56)	20.0 (19.2-20.6)	23.7 (22.8-24.3)	56 (53-60)	20.6 (20.0-21.2)	31.5 (30.8-32.2)	0.5 (0.3-0.5)	-	31.6 (30.6-32.6)	0.5 (0.4-0.5)
	Afternoon	22.0 (20.8-25.0)	52 (41-58)	19.9 (19.0-23.1)	23.9 (22.9-24.9)	57 (48-58)	21.0 (20.5-21.2)	32.1 (31.0-33.0)	0.5 (0.3-0.5)	-	32.1 (31.8-32.6)	0.5 (0.4-0.5)

Table 3. Output from the ANCOVA to test for the difference in skin temperature (T_{sk}) of the ring finger, forearm, cheek, forehead and the mean T_{sk} between children and care providers with WBGT indoor as covariate for the total period, winter and summer. *P*-values marked in bold are significant.

		Total period					Winter					Summer				
T_{sk}	Response variable	Sum of squares	df	Mean square	F	P-value	Sum of squares	df	Mean square	F	P-value	Sum of squares	df	Mean square	F	P-value
Ring finger	CC[a]	55.6	1	55.6	4.2	**0.041**	18.3	1	18.3	1.1	0.296	19.0	1	19.0	2.3	0.134
	WBGT	2367.5	1	2367.5	178.4	**<0.001**	1040.9	1	1040.9	62.3	**<0.001**	199.0	1	199.0	23.8	**<0.001**
Forearm	CC[a]	46.4	1	46.4	14.2	**<0.001**	36.1	1	36.1	8.4	**0.004**	17.8	1	17.8	10.0	**0.002**
	WBGT	407.6	1	407.6	124.6	**<0.001**	211.1	1	211.1	49.3	**<0.001**	63.2	1	63.2	35.6	**<0.001**
Cheek	CC[a]	131.0	1	131.0	52.8	**<0.001**	93.6	1	93.6	35.3	**<0.001**	47.0	1	47.0	28.5	**<0.001**
	WBGT	455.1	1	455.1	183.4	**<0.001**	385.4	1	385.4	145.6	**<0.001**	115.4	1	115.4	70.0	**<0.001**
Forehead	CC[a]	7.8	1	7.8	5.5	**0.019**	3.0	1	3.0	2.4	0.124	4.8	1	4.8	3.2	0.075
	WBGT	10.7	1	10.7	7.5	**0.006**	19.5	1	19.5	15.6	**<0.001**	5.4	1	5.4	3.6	0.060
Mean	CC[a]	4.6	1	4.6	1.4	0.233	8.3	1	8.3	2.0	0.158	1.3	1	1.3	0.8	0.362
	WBGT	987.4	1	987.4	308.5	**<0.001**	576.1	1	576.1	138.1	**<0.001**	77.1	1	77.1	50.4	**<0.001**

[a] Children/care providers

Table 4. Multilevel mixed-effects linear regression analysis for the relation between the mean skin temperature of the child ($T_{sk\ child}$) (model A) and care provider ($T_{sk\ cp}$) (model B) with selected independent variables, the relation between thermal sensation ranked by the care provider for themselves (TS_{cp}) with $T_{sk\ cp}$ (model C) and estimated for the children (TS_{child}) (model D) with $T_{sk\ child}$. All models are calculated for the total period and winter and summer separately.

			Total period		Winter		Summer	
Model	Dependent variable	Independent variable	Coefficient	SE[a]	Coefficient	SE[a]	Coefficient	SE[a]
A	Mean $T_{sk\ child}$	$WBGT_i$	0.68^{***}	0.14	0.72^{**}	0.22	0.60^{**}	0.16
		$WBGT_o$	-0.02	0.04	-0.10	0.11	0.08	0.05
		Clothing	0.86	1.13	-1.08	1.58	2.24	1.10
		Steps	-0.00^{*}	0.00	-0.00	0.00	-0.00	0.00
		BMI	0.01	0.11	0.03	0.15	-0.17	0.09
		Age	0.05^{*}	0.03	-0.03	0.44	0.01	0.02
		Sex	0.73^{*}	0.34	0.98^{*}	3.92	0.65^{*}	0.29
		Intercept	16.24^{***}	2.81	16.87^{***}	4.14	19.23^{***}	3.29
B	Mean $T_{sk\ cp}$	$WBGT_i$	0.44^{**}	0.13	0.27	0.21	0.53^{***}	0.13
		$WBGT_o$	0.02	0.04	0.22^{*}	0.09	0.06	0.05
		Clothing	0.88	0.86	-0.30	1.50	1.01	1.24
		Intercept	21.83^{***}	2.15	24.24	3.43	18.94^{***}	2.65
C	TS_{cp}	Mean $T_{sk\ cp}$	0.20^{***}	0.03	0.16^{***}	0.24	0.25^{**}	0.05
		Intercept	-5.67^{***}	0.99	-4.5^{***}	0.51	-7.39^{**}	1.45
D	TS_{child}	Mean $T_{sk\ child}$	0.03^{*}	0.01	0.01	0.01	0.04	0.03
		Intercept	-0.47	0.30	-0.11	0.33	-0.86	0.82

[a] Standard error

* p <0.05, ** p <0.01, *** <0.001

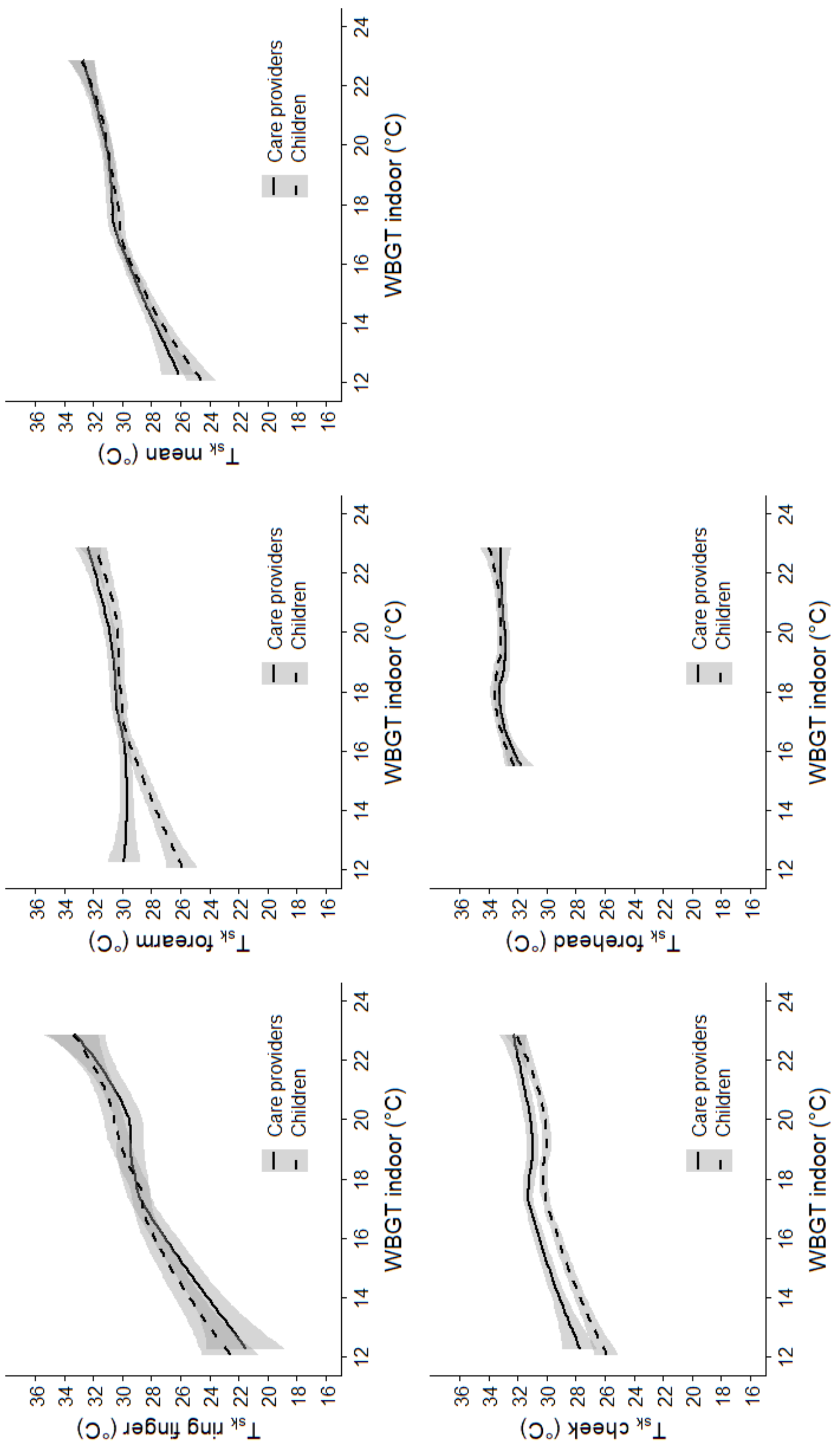


Figure 1. Skin temperature (T$_{sk}$) of the ring finger, forearm, cheek, forehead and the mean (mean ± 95% confidence interval) of the children (dashed lines) and care providers (solid lines) related to WBGT indoor. In two day-care centres T$_{sk}$ of the forehead was not measured during the winter, resulting in missing data for WBGT indoor between 12°C and 16°C.

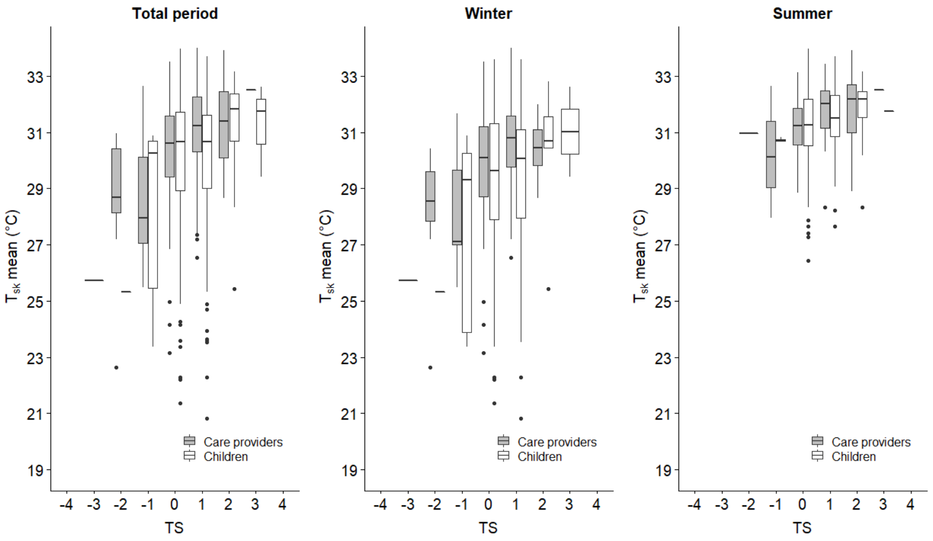


Figure 2. Boxplots of the thermal sensation score (TS) of care provider and the mean skin temperature (T$_{sk}$) and TS of the children estimated by the care provider compared to the mean T$_{sk}$ of the children. TS was ranked between -4 (very cold) and 4 (very hot). The box represents the interquartile range (IQR), the whiskers ±1.5 * IQR, the horizontal line within the box is the median and the black dots are outliers. In a few cases only a horizontal line is shown which means only one care provider mentioned that specific TS score.

Interviews

Fifty-three of the 58 care providers were able to complete the interviews. Table 5 shows the number of the care providers who gave a certain answer at each question subdivided into precautionary measures and knowledge. During days of low ambient temperatures most care providers (69.8%) answered they would put more clothes on the children as precautionary measure, followed by turning up the indoor heating (50.9%). During days of high ambient temperatures, most care providers (52.8%) answered they would give more (cold) drinks to the children or let them play with water outdoors (43.4%).

The most common answer on the first knowledge question; how the care providers notice a child is cold, was with feeling the child has cold skin (hands/feet) (50.9%), while in the heat the most answered symptom was by the red face of the child (67.9%). Furthermore, most care providers answered the question regarding the consequences of exposing a child to the cold or heat for too long with hypothermia (69.8%) and hyperthermia (71.7%) respectively. The most reported symptom of heat illness was a headache (24.5%), followed by tiredness (22.6%) and nausea or vomiting (22.6%). Twelve care providers (22.6%) could not name any symptom. The last question of the interview was if there is a difference between children and adults in how well they cope with extreme temperatures, which most care providers (71.7%) answered with that adults cope better with extreme temperatures.

Table 6 shows the knowledge rating of all the care providers and subdivided into care providers with some experience (SE; ≤ 5 years) and much experience (ME; >5 years) with working in day-care centres. From two care providers the amount of years' experience was unknown and therefore they were excluded from this part of the analysis. The care providers seem to be able to describe the signs of a child being cold or hot quite well based on this questionnaire with respectively 92.1% and 88.2% rated with sufficient knowledge, 3.9% and 9.8% with some knowledge and no one with no knowledge. Further, the care providers could name well what the consequences are of the exposure of a child to the cold or heat for too long with respectively 70.6% and 72.5% rated with sufficient knowledge and 23.5% and 19.6% with some knowledge. Only two (3.9%) care providers could not name the consequences of exposure of a child to the cold for too long. The care providers had more difficulties naming the symptoms of heat illness in children as only 13.7% were rated with sufficient knowledge, 62.7% with some knowledge and 23.5% with insufficient knowledge. Only 29.4% of the care providers did not know that children have more difficulties coping with extreme temperatures than adults. Care providers with more years of work experience in day-care centres had a higher percentage of sufficient knowledge and lower percentage of insufficient knowledge than care providers with less experience for five out of the six questions. Only on question 6; is there a difference between children and adults in how well they cope with extreme temperatures?, care providers with less experience had a higher percentage of sufficient knowledge than care providers with more experience with 59.3% vs 83.3% respectively.

Table 5. Number of care providers (%) providing a certain answer for each question asked during the interview. On Q1-Q7 care providers could provide multiple answers.

Question	**Answer**	**Amount care providers providing answer**
Precautionary measures		
Q1: What precautionary measures are taken in the day-care centre during cold days?	Add clothes	37 (69.8%)
	Turn up the indoor heating	27 (50.9%)
	Reduce playing time outdoors	15 (28.3%)
	Close windows/doors	8 (15.1%)
	Hot water bottle in children's bed	3 (5.7%)
	Drink warm fluids	1 (1.9%)
	Do not know	0 (0.0%)
	No answer / misunderstood	0 (0.0%)
Q2: What precautionary measures are taken in the day-care centre during hot days?	Provide more (cold) drinks	28 (52.8%)
	Play with water outdoors	23 (43.4%)
	Take clothes off	22 (41.5%)
	Open/close windows (depended on temperature difference)	19 (35.8%)
	Adjust time playing outside to cooler moments	18 (34.0%)
	Create shadow places outdoors	
	Window blinds	16 (30.2%)
	Air-conditioning/ventilator	16 (30.2%)
	Do not know	7 (13.2%)
	No answer / misunderstood	0 (0.0%)
		0 (0.0%)
Knowledge		
Q3: How do you notice a child is cold?	Cold skin (hand/feet)	27 (50.9%)
	Verbally express they are cold	20 (37.7%)
	Blue lips	19 (35.8%)
	Shivering	16 (30.2%)
	Crying	11 (20.7%)
	Reduced movement	7 (13.2%)
	Pale face	3 (5.7%)
	Want to sit on lap/cuddle	2 (3.8%)
	Chatter teeth	2 (3.8%)
	Wants to go indoors	2 (3.8%)
	Do not know	0 (0.0%)
	No answer / misunderstood	0 (0.0%)

Question	Answer	Amount care providers providing answer
Q4: How do you notice a child is hot?	Red face	36 (67.9%)
	Sweating	31 (58.5%)
	Sleepy/drowsy	13 (24.5%)
	Warm skin (hands/feet/forehead)	11 (20.7%)
	Crying	9 (17.0%)
	Take off clothes	9 (17.0%)
	Verbally express they are warm	8 (15.1%)
	Thirsty	5 (9.4%)
	Increased breathing	1 (1.9%)
	Do not know	0 (0.0%)
	No answer / misunderstood	0 (0.0%)
Q5: What can be the consequences when a child is exposed to the cold for too long?	Hypothermia	37 (69.8%)
	Child gets a cold / sick	9 (17.0%)
	Symptom of hypothermia (e.g., shivering/ adjusted breathing)	7 (13.2%)
	Do not know	2 (3.8%)
	No answer / misunderstood	1 (1.9%)
Q6: What can be the consequences when a child is exposed to the heat for too long?	Hyperthermia/heat stroke	38 (71.7%)
	Symptom of hyperthermia (e.g., dehydration/ drowsiness)	12 (22.6%)
	Do not know	0 (0.0%)
	No answer/misunderstood	3 (5.7%)
Q7: What are the symptoms of heat illness in a child?	Headache	13 (24.5%)
	Tiredness	12 (22.6%)
	Nausea/vomiting	12 (22.6%)
	Fainting	9 (17.0%)
	(absence of) sweating	8 (15.1%)
	Glowing/fever	7 (13.2%)
	Acting confused	7 (13.2%)
	Pale/red face	6 (11.3%)
	Dizziness	2 (3.8%)
	Do not know	12 (22.6%)
	No answer / misunderstood	0 (0.0%)
Q8: Is there a difference between children and adults in how well they cope with extreme temperatures?	Yes, children are more vulnerable	38 (71.7%)
	Yes, adults are more vulnerable	6 (11.3%)
	No	6 (11.3%)
	Do not know	3 (5.7%)
	No answer / misunderstood	0 (0.0%)

Table 6. Rating of the knowledge of the care providers based on six interview questions. Sufficient knowledge is defined as the care provider naming ≥ 2 symptoms in Q3 and Q4, or only cold skin, shivering, blue lips or chatter teeth on Q3 and only warm/pale/clammy skin on Q4, naming hypothermia in Q5 and hyperthermia in Q6, naming ≥ 3 symptoms in Q7, answered that adults cope better in Q8. Some knowledge is defined as the care provider naming 1 symptom in Q3 and Q4, naming symptoms of hypothermia in Q5 and of hyperthermia in Q6, naming 1 or 2 symptoms in Q7, some knowledge was not possible in Q8 as it is a right or wrong question. Insufficient knowledge is defined as the care provider naming 0 symptoms in Q3 and Q4, answering I do not know in Q5 and Q6, naming 0 symptoms in Q7 and answering that children and adults cope equally well of children cope better with extreme temperatures in Q8. The results are shown for all care providers and subdivided into care providers with some experience (SE) (≤5 years) and much experience (ME) (>5 years)

Knowledge questions	Sufficient knowledge (N)			Some knowledge (N)			Insufficient knowledge (N)			N.A.[a]		
	All	SE	ME	All	SE	ME	All	SE	ME	All	SE	ME
Q3: How do you notice a child is cold?	47	21 (87.5%)	26 (96.3%)	2	1 (4.2%)	1 (3.7%)	0	0 (0.0%)	0 (0.0%)	2	2 (8.3%)	0 (0.0%)
Q4: How do you notice a child is hot?	45	21 (87.5%)	24 (88.9%)	5	3 (12.5%)	2 (7.4%)	0	0 (0.0%)	0 (0.0%)	1	0 (0.0%)	1 (3.7%)
Q5: What can be the consequences when a child is exposed to the cold for too long?	36	15 (62.5%)	21 (77.8%)	12	7 (29.2%)	5 (18.5%)	2	2 (8.3%)	0 (0.0%)	1	0 (0.0%)	1 (3.7%)
Q6: What can be the consequences when a child is exposed to the heat for too long?	37	15 (62.5%)	22 (81.5%)	10	7 (29.2%)	3 (11.1%)	0	0 (0.0%)	0 (0.0%)	4	2 (7.4%)	2 (7.4%)
Q7: What are the symptoms of heat illness in a child?	7	1 (4.2%)	6 (22.2%)	32	13 (54.2%)	19 (70.4%)	12	10 (41.7%)	2 (7.4%)	0	0 (0.0%)	0 (0.0%)
Q8: Is there a difference between children and adults in how well they cope with extreme temperatures?	36	20 (83.3%)	16 (59.3%)	-	-	-	15	4 (16.7%)	11 (40.7%)	-	-	-

[a] No answer or misunderstood question

2.5. DISCUSSION

Young children are mostly dependent upon adults with regard to behavioural thermoregulation. As their thermophysiological responses may be insufficient compared to adults it is important that adults can accurately estimate the thermal state of their dependent child and act accordingly. To our knowledge this is the first study to assess care providers estimation of children's thermal state in day-care centres. As care providers of children, who are unable to clearly express their thermal state due to age-related inability, limited vocabulary and inexperience, it is important to be able to recognize when children are at risk of temperature related illnesses. Therefore, this study also aimed to assess the knowledge of the care providers regarding the thermoregulation of children and temperature related illnesses.

2.5.1. Thermal state

The current study showed significant differences in T_{sk} of the ring finger, forearm, cheek and forehead between the children and care providers, with the T_{sk} of the forearm and the cheek of the children consistently lower and of the ring finger and forehead consistently higher than the care providers. These differences in local T_{sk} between the children and care providers are in line with previous research where differences in local T_{sk} from early childhood into adulthood were reported (107). Activity level, clothing and BMI were reported to possibly account for these differences (107). In the current study however, next to indoor WBGT, which has the largest effect on T_{sk} of both the children and care providers, only sex, age and activity level seemed to influence T_{sk} of the children. No influence of clothing and BMI was found. A potential explanation for this may be that the locations where T_{sk} was measured in this study were mostly uncovered by clothing. Furthermore, BMI tended to influence T_{sk} locations where an increase of BMI was more apparent, like the upper chest and abdomen (107), which were not included in this study.

The local differences in T_{sk} in the current study between the children and care providers might also be due to physiological differences. Another study reported higher local T_{sk} in children of 9 years old compared to children of 13 years old while exercising at a similar relative intensity, which may be due to a lower sweat rate in the younger children (108). However, as activity level and clothing in the current study were not matched, we cannot state that the difference in local T_{sk} was mainly due to physiological differences. Therefore, future studies should focus on comparing regional distribution of local T_{sk} between young children and adults while matching for activity level and clothing to get a better understanding if the differences have a physiological or behavioural origin.

We found no differences in mean T_{sk} between the children and care providers and therefore the thermal state is considered to be similar. This is contrary to what was expected, since it was hypothesized that the thermal state of children would be different than the thermal state of adults. However, the thermal conditions in the current study were less extreme than expected beforehand with an indoor WBGT between 12°C and 23°C. Previous studies showed that children are predominantly more at risk at extreme low or high temperatures and that their thermoregulation is similar to adults during moderate thermal conditions (90). This may explain why in the current study no differences in thermal state between the children and care providers were found. Future studies should include a wider range of ambient temperatures.

2.5.2. Estimating thermal state

Whilst thermal state was found to be similar between the children and care providers, the results of this study show that the care providers did not correctly estimate the thermal state of the children in line with the second hypothesis. A significant relation was found between mean T_{sk} and TS_{cp} for the total period, as well as for winter and summer separately. However, the relation between T_{sk} and TS_{child} for the total period was significant, but for winter and summer separately insignificant. As care providers estimate the thermal state of a child within a small time frame and act accordingly, it seems more important that they are able to correctly estimate the thermal state of the child within a season than over the total period. For instance, a previous study showed that a mean T_{sk} higher than 32°C, measured at the same locations as this study, typically matches with a neutral to hot thermal sensation (102). In the current study, on multiple occasions care providers reported the thermal sensation of children with a mean T_{sk} lower than 25 °C as 'neutral' or 'slightly warm' (see figure 2), which possibly results in an incorrect behavioural action of the care provider to adjust the thermal environment in such a way to make it more comfortable.

Furthermore, a study comparing the thermal comfort of 4 and 5 year old children with adults reported the children felt overall 'slightly warmer' than the adults, most likely due to the difference in metabolic rate (109). Therefore, dressing the children with similar clothing as yourself as care provider or adult, or adjusting the room temperature for your own thermal comfort is most likely not optimal for the child.

2.5.3. Interviews

Care providers were asked what kind of precautionary measures were taken in the day-care centres to reduce cold and heat exposure to get an overview of the policies employed. Most answers relating to precautionary measures during days of high ambient temperatures were in line with the advice provided by The Netherlands National Institute for Public Health and the Environment (Dutch: RIVM) (110). Surprisingly, air conditioning or fans are not used much with only 13.2% of the care providers mentioning it as a precautionary measure during hot days. Not many guidelines are provided by the RIVM regarding days with low ambient temperatures. The focus is mainly on maintaining the temperature indoors at 20°C and in the bedrooms of the children between 15°C and 18°C. With 50.9% of the care providers answering they would turn up the indoor heating during cold days this was also one of their main focus areas.

Six different questions were asked during the interview to get an overview of care providers knowledge regarding thermoregulation and temperature related illnesses in children. The care providers reported many signs of a child being cold or hot with 92.1% and 88.2% (respectively) rated with sufficient knowledge on these questions. This finding is surprising since the results of this study also showed large variations in the care providers estimation of the thermal state of the children. A reason for this might be that some of the signs listed by the care providers for being cold (e.g., blue lips, chatter teeth, shivering) or hot (e.g., sweating, behaving sleepy or drowsy, thirsty) are only present when a child is very cold or hot, whilst in the current study that probably was not the case since the ambient conditions were fairly moderate. Furthermore, the care providers could name the consequences of exposing a child for too long to the cold and the heat quite well with respectively 94.1% and 92.1% sufficient or some knowledge. However, some of the care providers were not always able to name all the symptoms of heat illness with only 13.7% rated with sufficient knowledge on this question and 23.5% who could not name any symptoms. Also, 29.4% of the care providers believed there was no difference in how well children and adults cope with extreme temperatures or believed that children actually cope better. The outcome of the last two questions is quite worrying since the risk for children getting heat illness increases with more and more days of extreme ambient temperatures due to climate change (92).

A clear difference in the knowledge of the care providers existed, with many years of experience (>5 years) working in day-care centres compared to care providers with less experience (≤5 years). On every question, except the question about the difference between children and adults in coping with extreme temperatures, the care providers with more experience were rated with more knowledge. This may be due to the lack of attention for the effect of temperature on children in the education of care providers as mentioned several times during the interviews.

2.5.4. Limitations

In this study only T_{sk} was used to represent the thermal state of the children and care providers and core temperature was not measured. It has previously been shown that thermal sensation is strongly influenced by and can be predicted well with T_{sk} (101, 102). This has clearly been demonstrated in healthy adults, but it has not been systemically shown in children as thermophysiological data of children is limited. As such we have assumed that the thermal state of each child is also dependent upon their mean T_{sk} as demonstrated in adults. Furthermore, the accuracy of the thermometer used to measure T_{sk} in this study is limited with 2.5°C according to the specifications of the device. However, a comparison with an iButton showed a deviation of 0.3 ± 0.5°C (mean ± SD) in the range T_{sk} observed in this study. Nevertheless, additional research in this area may consider more sensitive devices to provide greater accuracy. Furthermore, as the thermal conditions were not quite extreme, the children and care providers were most likely in the thermoneutral zone and their core temperature did not vary that much (111). Therefore, T_{sk} was in this study most likely the main driver of thermal sensation. However, more research is warranted to investigate this, especially if more extreme thermal conditions are used. The analysis and rating of the answers of the care providers on the interviews was completed to the best of our knowledge, and decisions were made cautiously and after a thorough discussion. However, as there is no standardized way available to analyse such questionnaires, it should be considered that the choices made potentially influenced the results. Furthermore, the current study was executed in day-care centres, whilst children spend of course most of their time at home with their parents. It may be the case that parents know less about the effect of the heat on children than care providers in a day-care centre since in general they had no education regarding this topic at all. Future studies should focus on parents and the situation at home.

2.5.5. Conclusion

Thermal state of care providers was related to their thermal sensation, but the thermal state of children was unrelated to the assessed thermal sensation by the care providers. As thermoregulatory mechanisms are not fully developed at a young age and care providers had difficulties naming the correct symptoms of heat illness, the risk of temperature related illnesses is elevated. It is recommended to train care providers in thermal assessment, in particular novice care providers that appear to have less awareness on this topic.

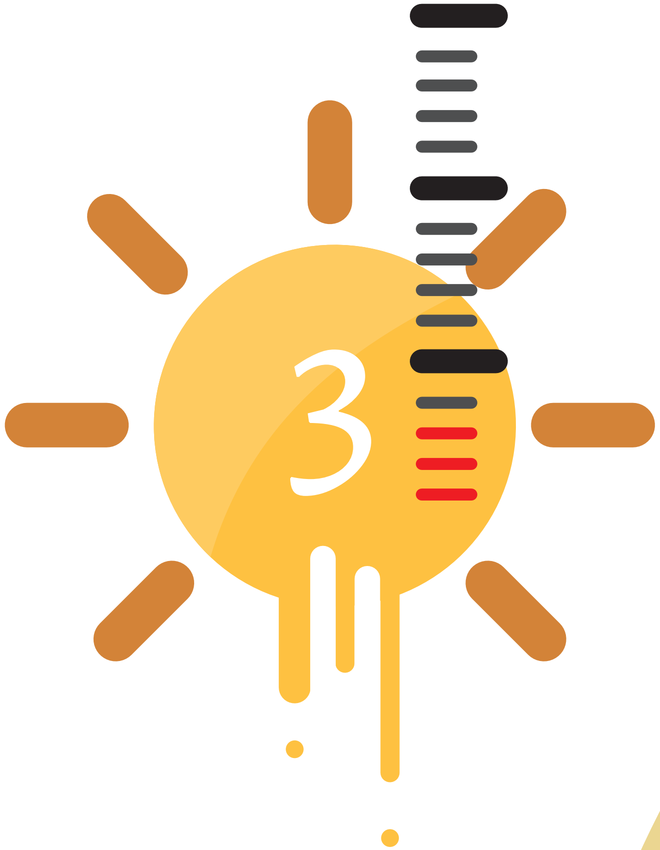
APPENDIX A

Questionnaire
Part 1: Precautionary measures
What precautionary measures are taken in the day-care centre during cold days?
What precautionary measures are taken in the day-care centre during hot days?
Part 2: Knowledge
How do you notice that a child is cold?
How do you notice that a child is hot?
What can be the consequences when a child is exposed to the cold for too long?
What can be the consequences when a child is exposed to the heat for too long?
What are the symptoms of heat illness in a child?
Is there a difference between children and adults in how well they cope with extreme temperatures?

APPENDIX B

Assessment knowledge care providers

Question	Correct answer	Rating			
		Sufficient knowledge	Some knowledge	Insufficient knowledge	N.a.
How do you notice a child is cold?	Signs mild hypothermia • Pale skin • Cold skin • Shivering • Increased heart rate/breathing • Drowsiness • Confusion (112, 113) Other named signs • Blue lips • Chatter teeth • Crying • Add clothes • Want to cuddle/sit on lap • Want to go inside • Reduce movement	≥ 2 signs, or only cold skin, shivering, blue lips or chatter teeth	1 sign	0 signs	No answer or misunderstood question
How do you notice a child is hot?	Signs mild heat illness • Pale/clammy skin • Sleepy/drowsy • Fewer wet nappies than normal • Dark urine • Refusing to drink • Intense thirst • Dry skin/mouth/eyes (89, 114) Other named signs • Crying • Take of clothes • Say their warm • Red face • Increased breathing	≥ 2 signs, or only warm skin or pale/clammy skin	1 sign	0 signs	No answer or misunderstood question
What can be the consequences when a child is exposed to the cold for too long?	Hypothermia or similar	Hypothermia or similar	Sign of hypothermia	Wrong answer or did not know the answer	No answer or misunderstood question
What can be the consequences when a child is exposed to the heat for too long?	Hyperthermia or similar	Hyperthermia or similar	Sign of hyperthermia	Wrong answer or did not know the answer	No answer or misunderstood question
What are the symptoms of heat illness in a child?	Neurologic • Dizziness • Headache • Confusion • Fatigue Gastrointestinal • Vomiting • Diarrhea Musculoskeletal • Muscle cramps Cardiopulmonary • Tachycardia • Tachypnea Skin • Sweating • Flushed • Warm (89)	≥ 3 symptoms	1-2 symptoms	0 symptoms	No answer or misunderstood question
Is there a difference between children and adults in how well they cope with extreme temperatures?	Yes, children are more vulnerable for extreme temperatures than older adults (41, 46, 87-89)	Yes, children are more vulnerable	N.a.	No or adults are more vulnerable	No answer or misunderstood question



Chapter 3

Metabolism- and sex-dependent critical WBGT limits at rest and during exercise in the heat

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3.1. ABSTRACT

Critical environmental limits are environmental thresholds above which heat gain exceeds heat loss and body core temperature (T_c) cannot be maintained at equilibrium. Those limits can be represented as critical wet-bulb globe temperature ($WBGT_{crit}$), a validated index that represents the overall thermal environment. Little is known about $WBGT_{crit}$ at rest and during low-to-moderate intensity exercise, or sex differences in $WBGT_{crit}$, in unacclimated young adults. The following hypotheses were tested: (1) $WBGT_{crit}$ progressively decreases as metabolic heat production (M_{net}) increases, (2) no sex differences in $WBGT_{crit}$ occur at rest, and (3) $WBGT_{crit}$ is lower during absolute-intensity exercise but higher at relative intensities in women compared to men. Thirty-six participants (19M/17W; 23±4 yr) were tested at rest, during light, absolute-intensity exercise (10 W), or during moderate, relative-intensity exercise (30% $\dot{V}O_{2max}$) in an environmental chamber. Dry-bulb temperature was clamped as relative humidity or ambient water vapor pressure was increased until an upward inflection was observed in T_c (rectal or oesophageal temperature). Sex-aggregated $WBGT_{crit}$ was lower during 10 W (32.9±1.7°C, $P<0.0001$) and 30% $\dot{V}O_{2max}$ (31.6±1.1°C, $P<0.0001$) exercise vs. rest (35.3±0.8°C), and lower at 30% $\dot{V}O_{2max}$ vs. 10 W ($P=0.01$). $WBGT_{crit}$ was similar between sexes at rest (35.6±0.8°C vs. 35.0±0.8°C, $P=0.83$), but lower during 10 W (31.9±1.7°C vs. 34.1±0.3°C, $P<0 .01$) and higher during 30% $\dot{V}O_{2max}$ (32.4±0.8°C vs. 30.8±0.9°C, $P=0.03$) exercise in women vs. men. These findings suggest that $WBGT_{crit}$ decreases as M_{net} increases, no sex differences occur in $WBGT_{crit}$ at rest, and sex differences in $WBGT_{crit}$ during exercise depend upon absolute vs. relative intensities.

3.2. INTRODUCTION

During heat stress, body core temperature (T_c) equilibrates proportionally to metabolic heat production across a wide range of environmental conditions (i.e., compensable heat stress) (115, 116). Hot environments that force T_c out of equilibrium result in a continuous rise in T_c (i.e., uncompensable heat stress) (115, 116). Belding and Kamon (117) developed a time-intensive protocol to determine critical ambient water vapor pressures (P_a), the ambient water vapor pressure above which heat balance cannot be maintained, for a variety of ambient temperatures, exercise intensities, and air velocities (117). An alternative to presenting the thermal environment as combinations of dry bulb temperature (T_{db}) and P_a is the wet-bulb globe temperature (WBGT). The WBGT provides a single temperature that represents the overall thermal environment, accounting for ambient temperature, humidity, radiation, and wind speed, the major determinants on thermal interactions between humans and their environment (118, 119). The WBGT is an ecologically valid thermal index, included in ISO7243, and currently used by industry, sport, and the military for the assessment of heat stress because of its simplicity and validity (e.g., (16, 120)).

The critical WBGT limit ($WBGT_{crit}$) is the WBGT above which T_c equilibrium (thermal balance) cannot be maintained, and T_c continues to rise for a given exercise intensity. The $WBGT_{crit}$ for acclimatized men and women in different industrial work ensembles during light to moderate metabolic work rates have been well-defined (121-123). However, $WBGT_{crit}$ values for unacclimatized men and women at rest and during light-to moderate-intensity exercise have not been established.

Sex differences in body size, aerobic fitness, and thermoregulatory function may lead to differences in $WBGT_{crit}$ between men and women. Women have a larger surface area-to-mass ratio than men, which leads to a greater heat dissipation while exercising (62). Work intensity determines metabolic heat production, the variable with the greatest impact in the heat balance equation (65, 123). In general women have a lower maximal aerobic capacity ($\dot{V}O_{2max}$) than men (66, 67). Therefore, women are often at a higher percentage of their $\dot{V}O_{2max}$ when working at an absolute exercise intensity compared to men. Conversely, when working at the same relative exercise intensity, i.e., $\%\dot{V}O_{2max}$, women are typically working at a lower absolute intensity, and therefore a lower metabolic heat production (68), compared to men. Further, men have a higher whole body sweat rate compared to women when near maximal sweating is required (62, 124, 125). Due to these differences in metabolic heat production and sweat rate, there may be sex differences in $WBGT_{crit}$. However, to our knowledge, there has yet to be an investigation of sex differences in $WBGT_{crit}$ at rest or during exercise at industry-relevant absolute and relative work intensities.

The purpose of the present investigation was to establish $WBGT_{crit}$ at rest, during light, absolute-intensity exercise (10 W), and during moderate, relative-intensity exercise (30% $\dot{V}O_{2max}$) in unacclimated young men and women. A secondary aim was to examine potential sex differences in $WBGT_{crit}$ at these energy expenditures. We hypothesized that (1) $WBGT_{crit}$ would be progressively lower as metabolic heat production increased from rest to moderate-intensity exercise, (2) men and women would have a similar $WBGT_{crit}$ at rest, and (3) women would have a lower $WBGT_{crit}$ compared to men during absolute-intensity exercise (10 W), but a higher $WBGT_{crit}$ during relative-intensity exercise (30% $\dot{V}O_{2max}$).

3.3. METHODS

3.3.1. Subjects

Data were collected at two locations; the Pennsylvania State University and the Vrije Universiteit Amsterdam in the Netherlands. All experimental procedures received ethics approval from the respective institutions and conformed to the guidelines set forth by the Declaration of Helsinki. After all aspects of the experiment were explained, oral and written informed consent was obtained.

Thirty-six healthy men and women (19 men/17 women) aged 18 to 35 yr were tested in one or two conditions. All subjects were healthy, normotensive (blood pressure was measured using brachial auscultation after 10 min quiet rest), non-smokers, and not taking any medications that might affect the physiological variables of interest in this study. No attempt was made to control for menstrual status or contraceptive use. To control for acclimation status, participants were excluded if they were physically active in a warm environment for at least one week consecutively within the two months prior to their experimental visits. For subjects who performed experimental trials at 30% $\dot{V}O_{2max}$, $\dot{V}O_{2max}$ was determined with the use of open-circuit spirometry (Parvo Medics TrueOne® 2400, Parvo, UT, USA) during a maximal graded exercise test performed on a motor-driven treadmill. For all other subjects, 16 in total, $\dot{V}O_{2max}$ was estimated using the YMCA submaximal cycle ergometer test (126) (Lode Excalibur, Groningen, The Netherlands). During the experiments, clothing was standardized with subjects wearing thin, short-sleeved cotton tee-shirts, shorts (30% $\dot{V}O_{2max}$ trials) or pants (rest and 10 W trials), socks, and walking/running shoes. For consistency with previous studies that have used similar clothing ensembles and according to the American Conference of Governmental Industrial Hygienists (ACGIH) guidelines for determining the effective WBGT (127, 128), no clothing corrections were made.

3.3.2. Testing Procedures

Upon arrival at the laboratory, participants provided a urine sample to ensure euhydration, defined as urine specific gravity ≤ 1.020 (USG; PAL-S, Atago, Bellevue, WA, USA) (129). All experiments were conducted in an environmental chamber with T_{db} held constant at 38°C. Subjects either (1) rested in a chair, (2) cycled on a cycle ergometer (Lode Excalibur, Groningen, The Netherlands) at a work rate of 10 W while maintaining a cadence of 70-90 RPM, or (3) walked on a motor-drive treadmill at a speed and grade that approximated 30% of their $\dot{V}O_{2max}$. Two subjects walked on a treadmill at a work rate approximating 10 W (established using the formula for external work during treadmill walking, as described under *Measurements*), with metabolic heat production matched to the 10 W cycling trials, and their data were included in the 10 W exercise data set. Because no differences were observed in metabolic heat production or critical environmental limits between subjects who either walked or cycled at 10 W, differences in heat loss between modalities were considered negligible. Subjects completed 1-2 trials in random order. The distribution for subjects who completed each trial were: Rest, n = 16 (8 men, 8 women); 10 W, n = 15 (7 men, 8 women); 30% $\dot{V}O_{2max}$, n = 18 (9 men, 9 women). 7 men and 6 women completed both the rest and 10 W exercise trial. For those subjects who completed 2 trials, the experiments were conducted on separate days, with at least 48 hours between visits.

During the first 30 min of each experiment, the environmental chamber was set to either 38°C T_{db} and 40% relative humidity (RH; resting and 10 W exercise trials) or 38°C T_{db} and 9 mmHg P_a (30% $\dot{V}O_{2max}$ trials) to allow participants' T_c to equilibrate. After 30 min, RH or P_a was increased by 10% every 10 min or 1 mmHg every 5 min, respectively, until a clear rise in T_c was observed. With no forced air movement in the environmental chambers, air movement velocity has been measured at 0.2 - 0.45 m/s (130).

3.3.3. Measurements

In resting and 10 W exercise trials, rectal (T_{re}; 401 YSI Compatible Reusable Temperature Probe, Yellow Spring Instruments, Yellow Springs, Ohio, USA) and gastrointestinal (T_{gi}; myTemp, Nijmegen, Netherlands) temperature were measured simultaneously. The rectal probe was inserted 10 cm past the anal sphincter. For T_{gi}, intestinal temperature capsules were swallowed one hour before the experiment (131). During the 30% $\dot{V}O_{2max}$ trials, oesophageal temperature (T_{es}) was measured with a probe made from a thermistor sealed in a paediatric feeding tube. The probe was inserted nasally and lowered in the oesophagus to the level of the left atrium, ~0.25 of the subject's standing height. Intraclass correlation (ICC) for the determination of $WBGT_{crit}$ between T_{re} and T_{gi} was 0.94 (Figure 1), suggesting excellent reliability for the determination of the T_c inflection point observed at critical environmental limits regardless of the method used to measure T_c. Similarly, extensive pilot data from the Penn State (unpublished, M.S. Hitscherich thesis) and Netherlands laboratories have demonstrated good to excellent reliability for inflection points in T_{es}, T_{re}, and T_{gi} during exercise in the heat, despite poor correlations in absolute temperature.

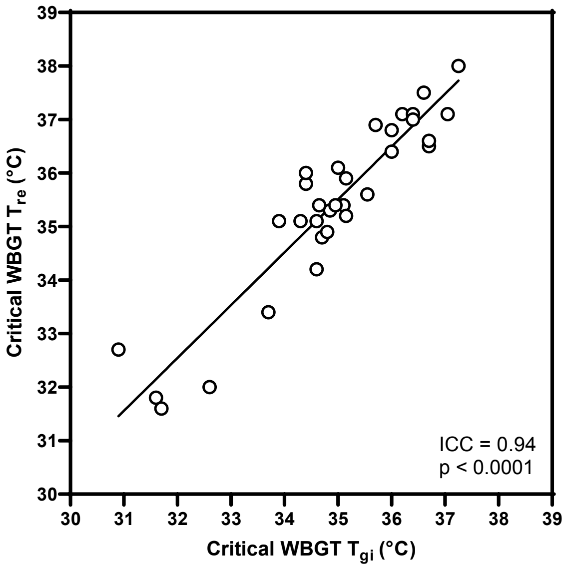

Figure 1. The correlation between critical WBGT limits determined using gastrointestinal temperature (T_{gi}) and rectal temperature (T_{re}).

Metabolic heat production (M; W/m²), normalized to body surface area, was calculated from $\dot{V}O_2$ (L/min) and the respiratory exchange ratio (RER; unitless) (132) as

$$M = \dot{V}O_2 \cdot \frac{\left[\left(\left(\frac{RER-0.7}{0.3}\right)\cdot 21.13\right) + \left(\left(\frac{1.0-RER}{0.3}\right)\cdot 19.62\right)\right]}{60} \cdot 1000 \cdot A_D^{-1} \qquad \textbf{Eq. 1}$$

where A_D is Dubois surface area (m²). External work (W; W/m²) was calculated as

$$W = 9.81 \cdot m_b \cdot v_w \cdot F_g \cdot A_D^{-1} \qquad \textbf{Eq.2}$$

where m_b is body mass (kg), v_w is walking velocity (m/min), and f_g is fractional grade of the treadmill (132). M_{net} was then calculated as M – W. For resting trials, $\dot{V}O_2$ and RER were assumed to be 3.5 mL/kg/min (133) and 0.80, respectively. For 10 W exercise trials, RER was assumed to be 0.85 and $\dot{V}O_2$ was estimated using the regression equation for $\dot{V}O_2$ during light cycling established by Reger et al. (134)

$$\dot{V}O_2 = 0.055P + 0.7815 \qquad \textbf{Eq.3}$$

where P is power output in watts. In 30% $\dot{V}O_2$max trials, $\dot{V}O_2$ and RER were measured for each participant using indirect calorimetry.

Sweat rate was determined from the loss of nude body mass on a scale accurate to ±20 g. Fluid intake was prohibited between the initial and final measurements of nude body mass.

3.3.4. Determination of WBGT_{crit}

A representative tracing of the time course of T_{es} and the environmental conditions for a typical test with increasing P_a is presented in Figure 2. An initial rise in T_c was observed that typically began to plateau after 30 – 40 min and remained at an elevated steady state as RH or P_a was systematically increased. The critical RH or P_a was characterized by the upward inflection of T_c from the elevated steady state, which was selected graphically from the raw data. A line was drawn between the data points, starting at the 30th min. A second line was drawn from the point of departure from the T_c equilibrium phase slope. The RH or P_a 1 min before the point at which the second line departed from the first was defined as the critical RH or P_a, respectively. Inflection points were chosen by two independent investigators naïve to the condition, group, and subject. The inter-rater reliability (ICC) was 0.93 for the T_c inflection point. The value included in the analysis was the average of the values determined by the two investigators. In the case of discrepancies >0.2°C between investigators, the analysis was repeated.

Psychrometric wet bulb temperature (T_{pwb}) at the T_c inflection point was determined using a standard psychrometric chart for critical P_a and RH experiments. Where necessary, T_{pwb} was converted to natural wet bulb temperature (T_{nw}) as (135).

$$T_{nw} = \frac{0.16(T_g - T_{db}) + 0.8}{200} * (560 - 2RH - 5T_a) - 0.8 + T_{pwb} \qquad \textbf{Eq. 4}$$

Where T_g is globe temperature. The WBGT at the T_c inflection point (i.e., the WBGT_{crit}) was calculated with the equation for indoor WBGT provided in ISO7243 (16):

$$WBGT = 0.7T_{wb} + 0.3\,T_g \qquad \textbf{Eq. 5}$$

Where T_{wb} and T_g were substituted for T_{nw} and T_{db}, respectively.

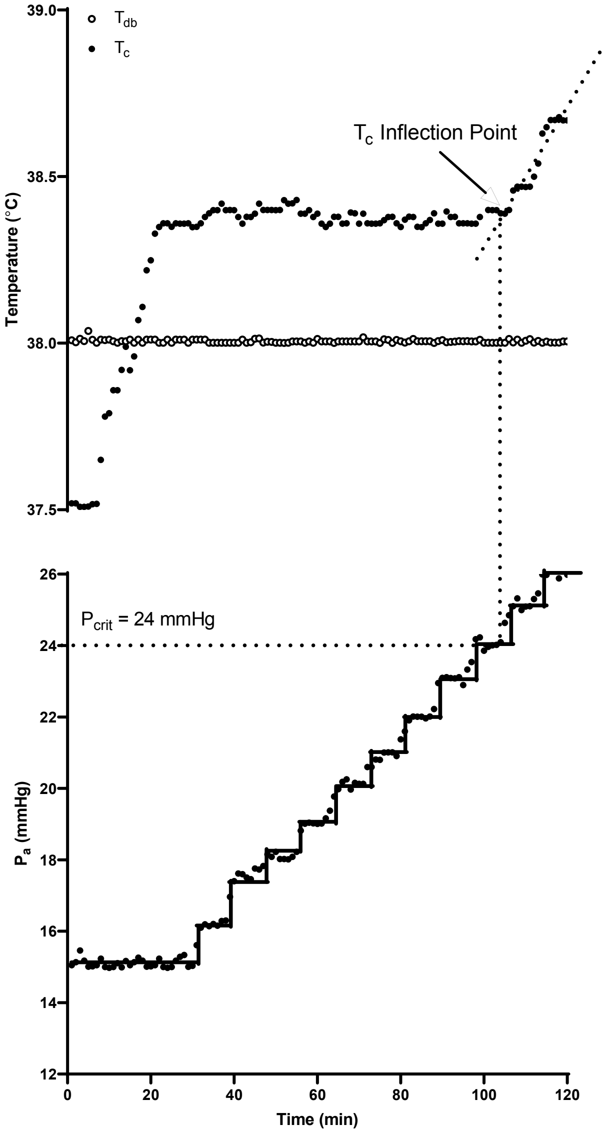

Figure 2. Representative tracing of the time course of oesophageal temperature (T_{es}), dry bulb temperature (T_{db}), and ambient water vapor pressure (P_a) for a 10 W exercise test with increasing P_a. Lines are drawn through data points in the lower panel to demonstrate the stepwise progression of P_a. The T_c inflection point represents the combination of environmental conditions above which heat stress becomes uncompensable and T_c equilibrium can no longer be maintained. In this case, the T_c inflection point occurs at P_a = 24 mmHg, resulting in a $WBGT_{crit}$ of 31.3°C.

3.3.5. Statistical Analysis

Student's unpaired t tests were used to compare subject characteristics. Paired samples t tests (SAS, version 9.4, SAS Institute, Inc., Cary, NC) were used to compare sex-aggregated $WBGT_{crit}$, metabolic heat production, and sweat rate data with metabolic intensity (i.e., rest, 10 W, or 30% $\dot{V}O_2$) as the independent variable. Similarly, within-sex differences in $WBGT_{crit}$, metabolic heat production, and sweat rate were analysed using paired samples t tests. Independent samples t tests were used to assess between-sex differences in $WBGT_{crit}$, metabolic heat production, and sweat rate. To account for multiple comparisons (3 comparisons per analysis), significance was accepted at $\alpha = 0.0167$. Hedges' g effect sizes, a corrected, unbiased measure of effect size for small samples (136), were calculated and reported when comparisons were statistically different (small effect = 0.2, medium effect = 0.5, large effect = 0.8). No a priori power calculation was performed. However, a post hoc power analysis using the effect size (g = 1.73) for the sex differences in $WBGT_{crit}$ during 10 W and 30% $\dot{V}$O2max exercise suggested that 7 subjects per group would provide adequate power (1-β = 0.84). Data are reported as means ± SD except in Figs. 3 and 4 which are presented as box-and-whisker plots with individual data points.

3.4. RESULTS

3.4.1. Subject Characteristics

Sex-aggregated and disaggregated subject characteristics are presented in Table 1. The men and women in this study were representative of the general population with respect to anthropometric characteristics and aerobic fitness (137). Thus, men were taller and had a higher mean $\dot{V}O_{2max}$ and body surface area (all $P < 0.05$), although the two groups were well-matched for surface area-to-mass ratio ($P = 0.25$). Importantly, there were no differences in $\dot{V}O_{2max}$, BMI, height, A_D, or $A_D \cdot kg^{-1}$ between groups that did each trial, although the group that completed the 30% $\dot{V}O_{2max}$ trials (21 ± 2) was significantly younger than the groups that completed rest (26 ± 3) and 10 W exercise (26 ± 4) trials (both $P < 0.0001$).

3.4.2. Metabolic Heat Production and Sweat Rate

Metabolic heat production and sweat rates at rest, during 10 W exercise, and during 30% $\dot{V}O_{2max}$ exercise, aggregated and disaggregated by sex, are presented in Table 2. M_{net} was higher during 10 W exercise compared to rest ($P < 0.0001$; $g = 9.48$) and was higher during exercise at 30% $\dot{V}O_{2max}$ compared to 10 W ($P = 0.01$; $g = 1.01$) and rest ($P < 0.0001$; $g = 9.47$).

Table 1. Subject Characteristics (mean ± SD)

	All (n = 36)	**Women (n = 19)**	**Men (n = 17)**
Age (yr)	23 ± 4	23 ± 4	23 ± 3
Height (m)	1.75 ± 0.1	1.66 ± 0.1	1.86 ± 0.1§
BMI (kg·m^{-2})	23 ± 3	22 ± 2	24 ± 3
A_D (m^2)	1.86 ± 0.20	1.68 ± 0.16	2.05 ± 0.15§
$A_D \cdot kg^{-1}$ (m^2·kg^{-1})	0.026 ± 0.002	0.026 ± 0.002	0.025 ± 0.002
$\dot{V}O_{2max}$ (ml·kg^{-1}·min^{-1})	45 ± 7	42 ± 7	48 ± 6§

A_D, DuBois body surface area; $A_D \cdot kg^{-1}$, body surface area to mass ratio. § P < 0.05 compared to women. Data were analysed using student's unpaired t tests.

In women, M_{net} was higher during exercise at 10 W ($P < 0.0001$; $g = 9.55$) and 30% $\dot{V}O_{2max}$ ($P < 0.0001$; $g = 12.06$) compared to rest, but was similar between 10 W and 30% $\dot{V}O_{2max}$ ($P = 0.48$). M_{net} was similarly higher in men during exercise at 10 W ($P < 0.0001$; $g = 13.29$) and 30% $\dot{V}O_{2max}$ ($P < 0.0001$; $g = 9.46$) compared to rest; however, in contrast to women, M_{net} was higher during exercise at 30% $\dot{V}O_{2max}$ compared to 10 W ($P = 0.001$). M_{net} was higher in men compared to women during exercise at 30% $\dot{V}O_{2max}$ ($P < 0.0001$), but was similar between sexes during rest ($P = 0.56$) and 10 W exercise ($P = 0.12$).

Sweat rates were similar between rest, 10 W exercise, and 30% $\dot{V}O_{2max}$ exercise for men ($P \geq 0.07$) and women ($P \geq 0.17$). Sweat rates were higher in men compared to women during exercise at 10 W ($P = 0.005$; $g = 1.76$) and 30% $\dot{V}O_{2max}$ ($P < 0.0001$; $g = 1.98$), but not rest ($P = 0.11$).

Table 2. Metabolic heat production adjusted for body surface area and sweat rates for all subjects and disaggregated by sex at rest and during 10 W and 30% $\dot{V}O_{2max}$ exercise (mean ± SD). Sex-aggregated and within-sex and comparisons were analysed using paired samples t tests. Between-sex comparisons were analysed using unpaired samples t tests. To account for multiple comparisons, significance was accepted at α = 0.0167. Sample sizes for men and women are included in parentheses for each condition.

	All	**Women**	**Men**
M_{net} (W·m^{-2})			
Rest (8M/8W)	43.8 ± 2.5	44.2 ± 2.8	43.4 ± 2.4
10 W (7M/8W)	138.9 ± 13.6*	144.1 ± 13.7*	133.1 ± 8.7*
30% $\dot{V}O_{2max}$ (9M/9W)	163.2 ± 30.2$^{*\#}$	138.7 ± 10.1*	188.8 ± 20.4$^{*\S\#}$
Sweat Rate (g·m^{-2}·h^{-1})			
Rest (8M/8W)	187.0 ± 58.7	163.4 ± 29.1	210.6± 72.5
10 W (7M/8W)	225.0 ± 64.4	181.1 ± 48.9	269.0 ± 45.7§
30% $\dot{V}O_{2max}$ (9M/9W)	207.3 ± 51.1	170.4 ± 33.1	244.2 ± 37.4§

M, men; VO2max, maximal oxygen consumption; W, women. * P < 0.0167 compared with rest; § P < 0.0167 compared with women; # P < 0.0167 compared with 10 W exercise.

3.4.3. Critical WBGT Limits

Figure 3 depicts $WBGT_{crit}$ at rest, 10 W exercise, and 30% $\dot{V}O_{2max}$ exercise. As expected, the $WBGT_{crit}$ was lower during exercise at 10 W (32.9 ± 1.7 °C; $P < 0.0001$; $g = 1.75$) and 30% $\dot{V}O_{2max}$ (31.6 ± 1.1 °C; $P < 0.0001$; $g = 3.59$) compared to rest (35.3 ± 0.8 °C). Further, the $WBGT_{crit}$ was lower during exercise at 30% $\dot{V}O_{2max}$ compared to 10 W ($P = 0.01$; $g = 0.90$).

Figure 4 illustrates sex-disaggregated $WBGT_{crit}$ at rest and during exercise at 10 W and 30% $\dot{V}O_{2max}$. In men, there was no difference in $WBGT_{crit}$ from rest (35.0 ± 0.8 °C) to 10 W exercise (34.1 ± 0.3 °C; $P = 0.58$), although the $WBGT_{crit}$ was lower during 30% $\dot{V}O_{2max}$ exercise (30.8 ± 0.9 °C) compared to rest ($P < 0.0001$; $g = 4.88$) or 10 W exercise ($P < 0.0001$ $g = 4.57$). In contrast, the $WBGT_{crit}$ was lower for women during exercise at 10 W (31.9 ± 1.7 °C; $P < 0.0001$; $g = 2.65$) and 30% $\dot{V}O_{2max}$ (32.4 ± 0.8 °C; $P < 0.0001$; $g = 3.70$) compared to rest (35.6 ± 0.8 °C), but there was no difference in $WBGT_{crit}$ between 10 W and 30% $\dot{V}O_{2max}$ exercise ($P = 0.97$).

There were no sex differences in $WBGT_{crit}$ at rest ($P = 0.14$). However, the $WBGT_{crit}$ during 10 W exercise was lower in women compared to men ($P = 0.01$; $g = 1.73$). Conversely, the $WBGT_{crit}$ during exercise at 30% $\dot{V}O_{2max}$ was lower in men compared to women ($P = 0.001$; $g = 1.73$).

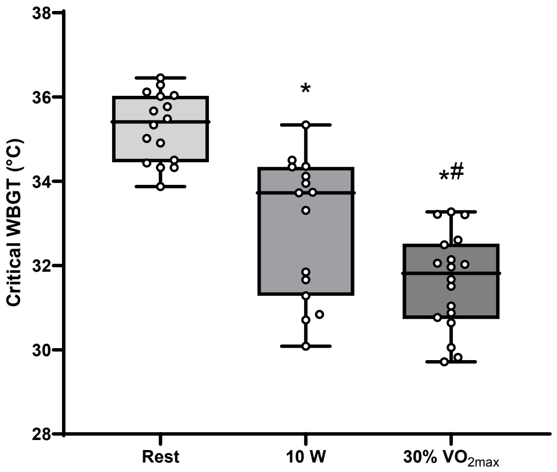

Figure 3. Sex-aggregated critical WBGT limits above which an equilibrium in core temperature can no longer be maintained during rest (n = 16), exercise at 10 W (n = 15), and exercise at 30% $\dot{V}O_{2max}$ (n = 18). Boxes represent first and third quartiles with median values denoted by the horizontal line, and whiskers indicate minimum and maximum observations. Data were analysed using paired samples t tests. To account for multiple comparisons, significance was accepted at α = 0.0167. * P < 0.0167 compared to rest; # P < 0.0167 compared to 10 W exercise.

Sex-aggregated and disaggregated environmental conditions (i.e., T_{db} and R.H.) at the T_c inflection point at rest and during 10 W and 30% $\dot{V}O_{2max}$ exercise are presented in Table 3. Differences in the critical R.H. for all subjects and when broken down by sex reflect differences in $WBGT_{crit}$ at rest and during 10 W and 30% $\dot{V}O_{2max}$ exercise.

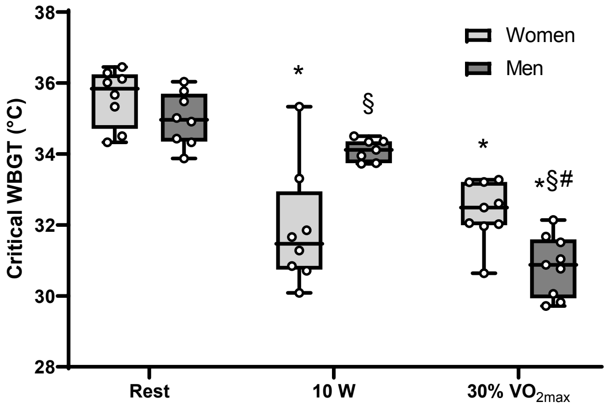

Figure 4. Sex differences in critical WBGT limits above which an equilibrium in core temperature can no longer be maintained during rest (Women, n = 8; Men, n = 8), exercise at 10 W (Women, n = 8; Men, n = 7), and exercise at 30% $\dot{V}O_{2max}$ (Women, n = 9; Men, n = 9). Boxes represent first and third quartiles with median values denoted by the horizontal line, and whiskers indicate minimum and maximum observations. Within-sex and between-sex comparisons were analysed using paired samples and unpaired samples t tests, respectively. To account for multiple comparisons, significance was accepted at $\alpha = 0.0167$. * $P < 0.0167$ compared to rest; § $P < 0.0167$ compared to women; # $P < 0.05$ compared to 10 W exercise.

Table 3. Dry bulb temperature (T_{db}) and relative humidity (R.H.) at the core temperature inflection point for all subjects and disaggregated by sex at rest and during 10 W and 30% $\dot{V}O_{2max}$ exercise (mean ± SD). Sex-aggregated and within-sex and comparisons were analysed using paired samples t tests. Between-sex comparisons were analysed using unpaired samples t tests. To account for multiple comparisons, significance was accepted at $\alpha = 0.0167$. Sample sizes for men and women are included in parentheses for each condition.

	All	**Women**	**Men**
T_{db} (°C)			
Rest (8M/8W)	37.9 ± 0.2	37.9 ± 0.2	38.0 ± 0.2
10 W (7M/8W)	38.2 ± 0.3	38.1 ± 0.2	38.2 ± 0.3
30% $\dot{V}O_{2max}$ (9M/9W)	38.1 ± 0.4	38.1 ± 0.4	38.1 ± 0.5
R.H. (%)			
Rest (8M/8W)	76.6 ± 7.3	79.4 ± 7.4	73.8 ± 6.5
10 W (7M/8W)	57.3 ± 11.4*	50.6 ± 11.9*	65.0 ± 3.2§
30% $\dot{V}O_{2max}$ (9M/9W)	48.9 ± 8.2$^{*\#}$	53.8 ± 7.1*	44.1 ± 6.3$^{*§\#}$

M, men; RH, relative humidity; Tdb, dry bulb temperature; VO2max, maximal oxygen consumption; W, women. * $P < 0.0167$ compared with rest; § $P < 0.0167$ compared with women; # $P < 0.0167$ compared with 10 W exercise.

3.5. DISCUSSION

To our knowledge, this is the first study to assess the $WBGT_{crit}$ for unacclimated young men and women at varying metabolic intensities ranging from rest to low- to moderate-intensity exercise. As expected, the $WBGT_{crit}$ progressively decreased as metabolic heat production increased. The $WBGT_{crit}$ was similar between men and women at rest, but sex differences were evident during exercise at 10W and 30% $\dot{V}O_{2max}$. During 10W exercise, the $WBGT_{crit}$ was higher in men compared to women. Conversely, the $WBGT_{crit}$ during exercise at 30% $\dot{V}O_{2max}$ was higher in women compared to men.

Unsurprisingly, the $WBGT_{crit}$ was highest at rest and declined progressively as exercise intensity, and thus M_{net}, increased. The 10 W exercise condition was chosen to approximate the metabolic intensity of activities of daily living, whereas the 30% $\dot{V}O_{2max}$ exercise condition was chosen because it reflects the intensity of many self-paced recreational activities and it is the intensity associated with an 8-h work day in many industrial settings (138). Thus, these data may effectively be used as safe WBGT limits (from a heat balance standpoint) during rest, activities of daily living, and recreational activity or industrial work for unacclimated young men and women.

Differences in $WBGT_{crit}$ at varying metabolic rates in acclimated young men and women have been previously described (123). The $WBGT_{crit}$ during exercise at 10W and 30% $\dot{V}O_{2max}$ were comparable to previously-reported $WBGT_{crit}$ values during and high metabolic rate conditions in acclimated young men and women (123). The similarities in $WBGT_{crit}$ at different metabolic rates between studies (i.e., lower metabolic rates in the current study) are most likely due to the acclimation status of the participants.

The absence of a sex difference in $WBGT_{crit}$ at rest is likely explained by similar whole body sweat rates and M_{net}. Sex differences in sweating are unlikely to manifest at low requirements for heat loss (139). Sex differences in $WBGT_{crit}$ were evident during absolute (10 W) and relative (30% $\dot{V}O_{2max}$) exercise intensity conditions, wherein women demonstrated lower and higher $WBGT_{crit}$ at 10 W and 30% $\dot{V}O_{2max}$ exercise, respectively. Sweat rates were lower in women compared to men during exercise at both intensities, similar to previous findings that sex differences in sweat rates mostly occur when the exercise intensity and ambient temperature are high enough that the requirements for sweating are near maximal to maintain thermal balance (62, 63, 140). In contrast, there was no difference in M_{net} between sexes when matched at an absolute work rate of 10 W, but M_{net} was lower in women compared to men during 30% $\dot{V}O_{2max}$ exercise. Because men and women differ in $\dot{V}O_{2max}$ on average, this results in lower absolute exercise intensities and M_{net} (68) for women when working at a fixed percentage of $\dot{V}O_{2max}$. Thus, sex differences at 10 W exercise reflect a true sex difference because the two groups were matched for M_{net}, and therefore the requirement for heat loss was equal. These findings differ from previous data that showed no sex differences in evaporative heat loss when the requirement for heat loss was below 300 $W \cdot m^{-2}$ (139). Conversely, the differences during 30% $\dot{V}O_{2max}$ exercise were primarily driven by reduced M_{net} and heat loss requirements for women. Systematic differences in the change in core temperature during exercise in the heat between age-, sex-, and acclimation-matched groups of different body mass and surface area are eliminated when subjects exercise at a fixed heat production per unit body mass (141) . However, it is unclear whether this would hold true in the current study when comparing sex differences in $WBGT_{crit}$.

Together, these data suggest that potential sex differences in $WBGT_{crit}$ depend upon acclimation status and whether work is being performed at a relative or absolute intensity. Importantly, most self-paced recreational activity and industrial work is likely performed at relative, rather than absolute, intensities (138, 142, 143). Recommendations of the International Organization for Standardization (ISO) are based on absolute metabolic rates; thus, the recommended WBGT limits recommended in ISO7243 may be overestimated for women, particularly those who are unacclimated (16). It is noteworthy that the differences between ISO recommendations and critical WBGT thresholds for women encompass the effect of body size, in addition to the physiological effect of sex, especially at higher metabolic intensities (64, 141, 144). Therefore, separate WBGT standards for unacclimated men and women during continuous work in the heat warrants consideration.

3.5.1. Limitations

Data were collected at two locations with minor differences in protocols. Namely, critical environmental limits were determined at rest and during the 10 W trials with stepwise increases in RH, whereas 30% $\dot{V}O_{2max}$ trials were conducted by increasing water vapor pressure. When converted to WBGT, however, either method results in relatively small increases in the thermal environment (i.e., 0.3 – 1.3°C increments) and are unlikely to influence the overall methodology which relies on the biophysics of heat exchange. These differences are therefore unlikely to result in significant systematic disparities in $WBGT_{crit}$. Similarly, subjects wore long pants in the Netherlands trials and shorts during the Penn State trials. This was considered to have a negligible effect on $WBGT_{crit}$ as ACGIH guidelines for determining the effective WBGT for various ensembles (127) does not necessitate implementation of a clothing correction factor for these conditions.

Metabolic heat production was estimated for rest and 10 W exercise. Resting metabolic heat production was estimated using well-accepted average values for $\dot{V}O_2$ and RER at rest (133), and those estimates closely aligned with empirically derived values previously reported (68). Metabolic heat production during 10 W exercise was estimated assuming an RER of 0.85 and using the regression equation for $\dot{V}O_2$ during light cycling established by Reger et al. (134). The accuracy of the calculated values was confirmed in a subset of subjects for whom $\dot{V}O_2$ and RER were measured via indirect calorimetry, yielding results that fell within the distribution of estimated values.

No attempt was made in this study to control for the menstrual cycle or contraceptive use of the female participants, which may influence core temperature in the women. However, although absolute core temperature varies across the menstrual cycle, the change in core temperature during exercise in the heat is unaffected (145). Likewise, the core temperature profiles during exercise in the heat were similar across menstrual phases. It is therefore unlikely that the $WBGT_{crits}$ observed in this study were influenced by not controlling for menstrual cycle.

Finally, the $WBGT_{crit}$ in the rest and 10W exercise conditions was determined using both T_{re} and T_{gi}, whereas T_{es} was measured during 30% $\dot{V}O_{2max}$ trials. Importantly, as shown in Figure 1, ICC analysis suggested excellent reliability (ICC = 0.97) between T_{re} and T_{gi}. We therefore concluded that, although the absolute value for T_c may vary, the $WBGT_{crit}$ is similar regardless of the method employed for measuring T_c.

3.5.2. Conclusion

The $WBGT_{crit}$ in unacclimated, healthy young men and women progressively decreases as exercise intensity and metabolic heat production increases. Sex differences in $WBGT_{crit}$ were not evident during rest, but were observed depending upon whether exercise was performed at an absolute or relative exercise intensity. The $WBGT_{crit}$ was lower in women compared to men during absolute-intensity exercise, but higher during relative-intensity exercise. These sex differences are most likely explained by differences in metabolic heat production and sweat rate. Future studies are warranted to investigate the $WBGT_{crit}$ in vulnerable populations with impaired thermoregulatory function, including older adults or those with various disease or disability states such as multiple sclerosis or spinal cord injury.

Chapter 4

Sex differences in temperature-related all-cause mortality in the Netherlands

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4.1. ABSTRACT

Purpose Over the last few decades, a global increase in both cold and heat extremes has been observed with significant impacts on human mortality. Although it is well-identified that older individuals (>65 years) are most prone to temperature-related mortality, there is no consensus on the effect of sex. The current study investigated if sex differences in temperature-related mortality exist in the Netherlands.

Methods Twenty-three-year ambient temperature data of the Netherlands were combined with daily mortality data which was subdivided into sex and three age classes (<65 years, 65-80 years, ≥80 years). Distributed lag non-linear models were used to analyse the effect of ambient temperature on mortality and determine sex differences in mortality attributable to cold and heat, which is defined as mean daily temperatures above and below the Minimum Mortality Temperature respectively.

Results Attributable fractions in the heat were higher in females, especially in the oldest group under extreme heat (≥97.5th percentile), whilst no sex differences were found in the cold. Cold- and heat-related mortality was most prominent in the oldest age group (≥80 years) and to a smaller extent in the age group between 65-80 years. In the age group <65 years temperature-related mortality was only significant for males in the heat.

Conclusion Mortality in the Netherlands represents the typical V- or hockey-stick shaped curve with a higher daily mortality in the cold and heat than at milder temperatures in both males and females, especially in the age group ≥80 years. Heat-related mortality was higher in females than in males, especially in the oldest age group (≥80 years) under extreme heat, whilst in the cold no sex differences were found. The underlying cause may be of physiological or behavioural nature, but more research is necessary.

4.2. INTRODUCTION

A global increase in heat waves and cold spells have been observed over the last few decades and this increase is expected to continue due to climate change (3, 146, 147). Although mild cold is reportedly the dominating cause of temperature-related mortality worldwide (148), thermal extremes have a profound effect on morbidity and mortality, mostly due to cardiovascular or respiratory failure (149-151). To inform policies that aim to limit temperature-related mortality, it is important to know which subgroups of the population are especially vulnerable to this cause of death. For example, it is well known that the elderly population are most at risk for temperature-related morbidity and mortality, as their thermoregulatory function is impaired, they are often less physically fit and have more chronic illnesses and diseases (152, 153).

Besides an age-related increase in risk for temperature-related morbidity and mortality, there might also be sex-related differences. Males and females differ from each other in their physiology, anthropometric characteristics, body composition and social behaviour, which impact their thermoregulation (63, 154). Females tend to have a disadvantage in the heat due to the larger body surface to mass ratio, greater body fat percentage and lower exercise capacity (154). Furthermore, in hot conditions, females have a decreased heat dissipation compared to males during intense exercise due to a lower sweating capacity (62). In the cold, females are at a slight advantage due to their greater body fat content which functions as insulation (154, 155). A higher heat-related mortality for females and a higher cold-related mortality for males is expected due to the aforementioned physiological differences.

A number of studies investigating temperature-related mortality suggest sex is a contributing factor, with females to be more at risk during the heat than males (39, 72, 156). However, this is not fully supported in the literature (39, 72, 156-158). In Stockholm County (Sweden), Hong Kong (China) and Wuhan (China) a higher mortality amongst males was reported in the heat (157-159). In different regions in Spain, three studies reported contrasting outcomes regarding sex differences in the heat. In Galicia, a higher mortality was reported amongst females (160), whilst in Catalonia no sex differences were reported (161). In Madrid, a higher mortality amongst males in the age group between 65-75 years, and higher mortality in females in the age group older than 75 years, were reported (162). In Hong Kong (China), Stockholm County (Sweden) and Cyprus, higher mortality in males was reported in the cold (157, 159, 163), while in South East England a higher mortality in females was reported (164). In seven USA cities (Denver, Detroit, Minneapolis, New Haven, Pittsburgh and Chicago, and Seattle) no difference between males and females was found in the cold (165). Differences in temperature related mortality between studies executed in different cities and countries may be partly related to geographical location and differences in the building environment. A previous study showed that the Minimum Mortality Temperature (MMT) is dependant on geographical location with southern European cities having a higher MMT than northern European cities (166). Urban areas are hotter than rural areas and in cities with tall and high density buildings with a lack of green spaces, temperatures can increase significantly more than in cities surrounded with rural areas and low buildings (167). Furthermore, structure and insulation of buildings differ between countries, which can influence the effect outdoor temperature has on the indoor temperature where people spend most of their time (168). However, this does not explain the lack of consensus in the literature on sex differences in temperature-related mortality, since the distribution of males and females within a city is similar. Furthermore, less information is available about the sex differences in mortality in the cold than in the heat. Therefore, the aim of the current study was to add information to the limited and sometimes contradictory pool of data on sex differences in temperature-related mortality by analysing a large dataset based on 23 years (1995 till 2017) of daily temperature and mortality in the Netherlands.

4.3. METHODS

4.3.1. Data sources

Daily mortality in the Netherlands between 1 January 1995 and 31 December 2017 was obtained from Statistics Netherlands. The data contains the daily all-cause mortality for the total Dutch population and is subdivided into sex and three age classes: <65 years, 65-80 years, ≥80 years. Daily population size for the different sexes and age classes were also included in the dataset. Temperature data were obtained from the Royal Netherlands Meteorological Institute. Hourly ambient temperature was derived from the five main weather stations throughout the Netherlands (De Bilt; Rotterdam; Schiphol Airport; Eelde and Maastricht) and averaged over time and space into average daily temperature. For the Netherlands this approach seemed acceptable as the Netherlands is rather small, 300km from north to south and 200km from west to east. Maximum distance from a household to the closest weather station included in the study is 100km. Correlations of the measured temperatures between the included weather stations is very high: namely $r>0.967$. Other studies performed in the Netherlands investigating mortality and temperature used the same approach with averaged daily temperature (169-171), which gives confidence in our approach for the Netherlands.

4.3.2. Statistical analysis

Data was analysed in the statistical software R version 3.6.1. Time series of daily death counts for males and females divided into the three age classes were analysed separately by quasi-Poisson regression allowing for over dispersion (172). Distributed lag non-linear models (DLNM) were fitted using the dlnm package (173) applying natural cubic spline functions with eight degrees-of-freedom per year for adjusting for seasonality and long-term trend. In order to consider non-linear temperature effects, a quadratic B-spline function with four degrees-of-freedom was used with two equally distributed internal knots placed at 0.8°C and 13.8°C in combination with another spline function with three logarithmically equally distributed knots to model lagged temperature effects up to 20 days (174). In addition, day-of-week was included as covariate and log population size as offset, i.e. as predictor with coefficient fixed to one.

Mortality due to the cold or heat is quantified by attributable fractions, which is the excess mortality calculated from the Minimum Mortality Temperature (MMT) (174). The MMT is the mean daily temperature at which the lowest mortality occurs and quantifies the threshold between the cold and heat mortality slope (175). The MMT with SE was calculated by a search algorithm over the fitted response function (176), which was applied separately for the time series defined by sex and age group. Heat is defined as ambient temperatures higher than the MMT and cold is defined as ambient temperatures lower than the MMT. A subdivision is made between mild and extreme cold and heat mortality attributable fractions, where mild cold and heat mortality attributable fractions are defined as the mortality between the MMT and $2.5^{th}/97.5^{th}$ percentile of the mean daily temperature, and extreme cold and heat mortality attributable fractions below and above the $2.5^{th}/97.5^{th}$ percentile (148).

From the calculated attributable fractions with SE, the presence of temperature-related mortality was deduced in case the attributable fraction 95% confidence interval (CI) did not include zero. The significance of sex as potential modifier of cold- and heat-related mortality was assessed by inspection of the confidence intervals for males and females.

4.4. RESULTS

Table 1 shows the descriptive statistics of daily mortality in the Netherlands between 1995-2017. In the Netherlands, females reach an older age than males as can be seen by the population sizes in table 1. Furthermore, the mean age of females is slightly higher than males; +0.3, +0.4 , +1.0 years for the age groups <65, 65-80, ≥80 years, respectively. Therefore, daily mortality per 100,000 residents of the same sex and similar age provides a better overview of sex differences in temperature-related mortality.

Mortality due to the cold was greater than to the heat in both males and females. In the cold there was in increase in mortality from the MMT to the 2.5^{th} percentile for males of 14.7% and for females of 18.3%. In the heat the increase in mortality from the MMT to the 97.5th percentile was 8.0% for males and 14.3% for females. The highest increase in mortality was in the oldest age group (≥80 years) with an increase for males and females of 19.2% and 21.9% respectively in the cold, and of 14.6% and 21.2% respectively in the heat. Especially in the heat there was a large difference between the oldest age group (≥80 years) and the age groups <65 and 65-80 years. This is also shown in figure 1 and 2. Figure 1 shows the overall exposure-response associations of daily mean temperature (°C) and daily mortality cumulating all lagged effects in the Netherlands between 1995-2017. Figure 2 shows the daily mortality attributable fractions in the heat and cold in the Netherlands between 1995-2017. Data are subdivided into males and females for the total population and separated for three different age groups (<65, 65-80, ≥80 years). In the age group <65 years temperature-related mortality was non-significant; only for males in the heat, there appears to be a small temperature effect on mortality, which was comparable in size to that for males aged 65-80 years.

Overall mortality per 100,000 residents was higher in males in the heat for the age groups 65-80 years and ≥80 years (table 1), but the increase in mortality from the MMT was higher for females with 4.0% and 4.4% in the age group 65-80 years and 14.6% and 21.1% in the age group ≥80 years for males and females respectively. Inspecting the confidence intervals for males and females in figure 2 indicates that in mild and extreme heat for the total population the differences between males and females were significant, but age-specific differences were significant only for the age group ≥80 years in extreme heat. No significant differences occurred in sensitivity to the cold between males and females.

Table 1. Distribution of daily mortality in total and per 100,000 residents in the Netherlands between 1995 – 2017 subdivided into sex and age group. The 2.5th and 97.5th percentile of the mean daily temperature represent the cut-off for respectively extreme cold and heat. Daily mortality shown for the 2.5th and 97.5th temperature percentiles, which represent cold and heat stress, respectively, are the averaged values below and above these percentiles, and daily mortality shown for the Minimum Mortality Temperature (MMT) is the averaged value within the standard error. Population size (N) and mean age (years),as well as the MMT and percentage changes in mortality the 2.5th and 97.5th percentile, respectively, compared to the MMT as estimated by the distributed lag non-linear model (DLNM) are shown per age group and sex.

Sex & age group	**Daily mortality**								**Population size (N)**	**Mean age (years)**	**MMT (Mean ± SE (°C))**	**Change MMT – 2.5th percentile (% (CI))**	**Change MMT – 97.5th percentile (% (CI))**
	2.5th percentile[a]		**Mean**		**MMT[b]**		**97.5th percentile[c]**						
	Total	**Per 100,000**	**Total**	**Per 100,000**	**Total**	**Per 100,000**	**Total**	**Per 100,000**					
Male													
Total	206	2.6	186	2.3	173	2.1	187	2.3	8,045,742	37.9	15.4 ± 0.4	14.7 (11.5 – 18.0)	8.0 (5.9 – 10.2)
<65	44	0.6	42	0.6	40	0.6	44	0.6	7,012,552	32.5	15.6 ± 7.5	2.4 (-3.5 – 8.7)	4.8 (0.6 – 9.1)
65-80	81	10.2	73	8.8	68	8.2	74	9.2	837,818	70.9	16.4 ± 1.6	17.9 (11.8 – 24.5)	4.0 (0.5 – 7.5)
≥80	80	42.8	71	36.2	63	32.2	69	36.5	195,373	84.2	14.8 ± 2.0	19.2 (14.1 – 24.5)	14.6 (10.9 – 18.5)
Female													
Total	216	2.7	196	2.6	183	2.1	203	2.5	8,212,706	40.0	15.1 ± 0.2	18.3 (15.1 – 21.6)	14.3 (12.0 – 16.6)
<65	30	0.4	29	0.5	28	0.4	30	0.4	6,830,253	32.8	15.7 ± 9.4	7.4 (0.0 – 15.4)	2.0 (-2.8 – 7.1)
65-80	55	5.7	51	5.7	48	4.9	52	5.4	983,848	71.3	16.1 ± 3.3	16.2 (9.0 – 23.9)	4.4 (0.2 – 8.8)
≥80	130	33.2	116	33.4	106	26.3	120	30.8	398,605	85.2	15.0 ± 0.2	21.9 (17.8 – 26.2)	21.1 (18.1 – 24.2)

[a] < -1.8°C

[b] Minimum Mortality Temperature

[c] > 21.5°C

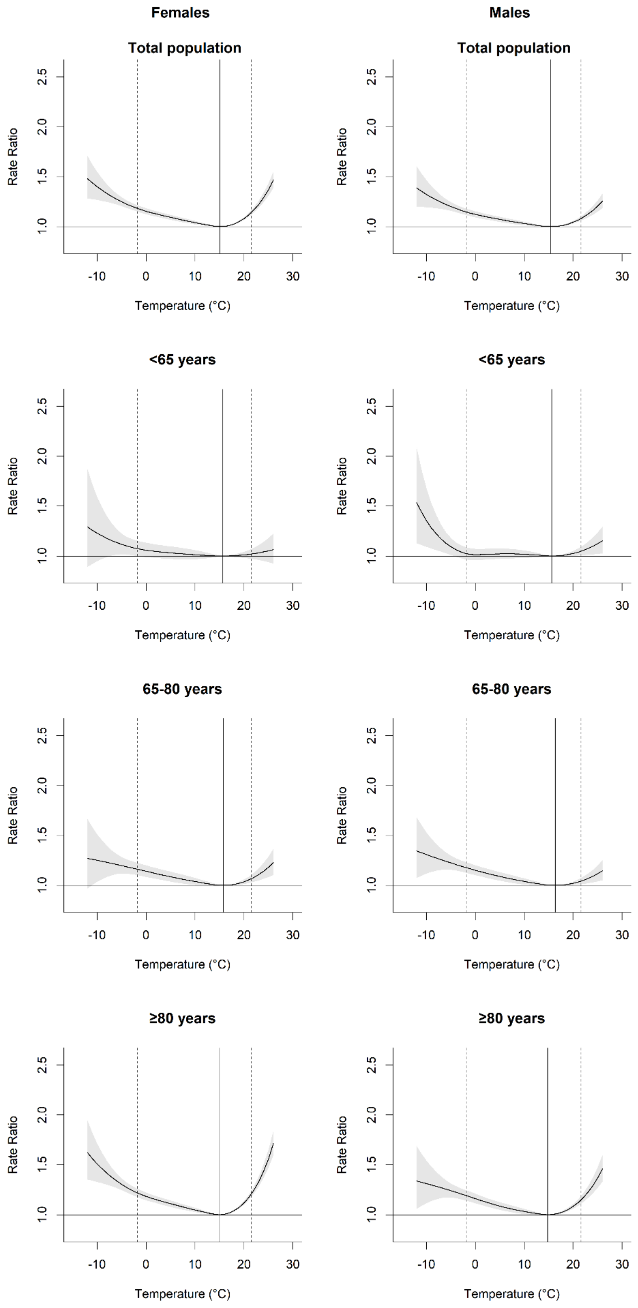

Figure 1. The overall cumulative exposure-response associations of daily mean temperature (°C) and daily mortality in the Netherlands between 1995-2017 subdivided into males and females for the total population and separated for three different age groups (<65, 65-80, ≥80 years). The vertical solid lines represent the Minimum Mortality Temperature (MMT) and the dashed lines the 2.5th and 97.5th percentile of the mean daily temperature, respectively. Grey-shaded error bands indicate the 95% confidence interval.

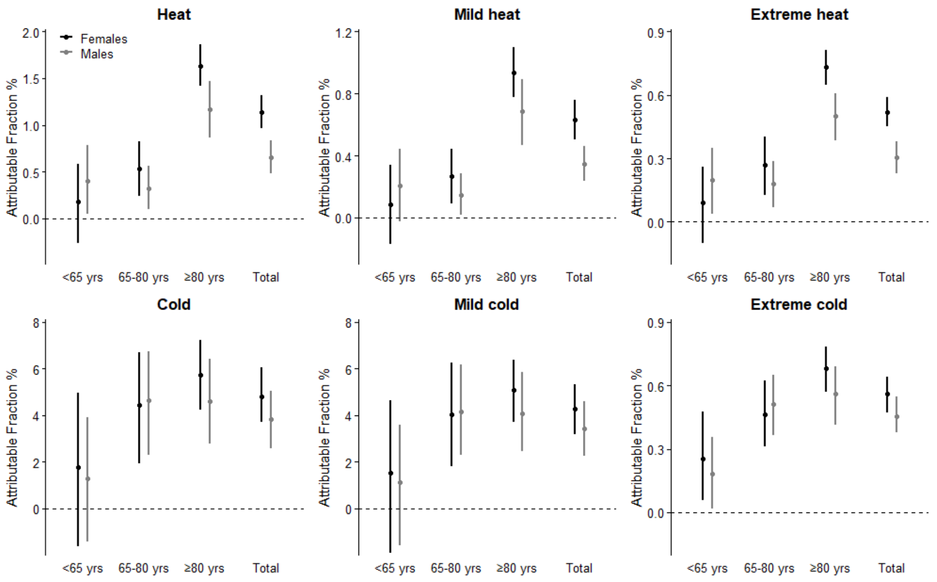

Figure 2. Daily mortality attributable to the heat and cold in the Netherlands between 1995-2017 subdivided into males and females for the total population and separated for three different age groups (<65, 65-80, ≥80 years). Heat is defined as ambient temperatures higher than the Minimum Mortality Temperature (MMT) and cold is defined as ambient temperatures lower than the MMT. Mild cold/heat is defined as the temperature between the MMT and 2.5th/97.5th percentile of the mean daily temperature, and extreme cold/ heat as the temperature below and above the 2.5th/97.5th percentile. Vertical error bars indicate the 95% confidence interval. Please note that the y-axes are not identically scaled.

4.5. DISCUSSION

Mortality in the Netherlands represents the typical V- or hockey-stick shaped curve with a higher daily mortality in the cold and heat than at milder temperatures in both males and females, especially in the age group ≥80 years. There were no sex differences in cold-related mortality in this study, but females appear to be more susceptible than males to both mild and extreme heat when considering all age groups combined. This is still the case after correcting for population size, which is important as females tend to live longer than males, which results in twice as many females than males in the Netherlands in the age group ≥80 years. Age-specific significant sex differences were only observed for the oldest group in extreme heat, but not in mild heat as for the total population, probably due to lower statistical power associated with fewer death events in the age-specific time series (276). These findings are in line with the majority of previous studies, from various cities/countries with different MMT and climates (156, 177-179). The MMT of different studies and countries can differ due to the analytical method used (175), but also because of differences in climate. The MMT decreases from southern to northern European countries and is strongly related to the mean ambient temperature (166). In the south of Europe the MMT can be as high as 26.5°C to 28°C, while in the north of Europe it can be as low as 16.0°C to 17.5°C (166). In the current study we even found an average MMT of 15.3°C. Different climates reported in previous studies are, for example, Hunan (China), which has a humid subtropical climate, Galicia (Spain), which has a mild oceanic climate and Belgrade (Serbia), which has a continental climate (160, 179-181). To our knowledge, this is the first study to explore sex differences in temperature-related mortality in a temperate marine climate, as observed in the Netherlands. Our results contribute to the existing body of literature and provide evidence that, alongside other climates, females appear to be more vulnerable to heat-related mortality.

The increasing risk for heat-related mortality as people age, may partly be explained by the age-related physiological changes. McGinn, Poirier (57) showed that whole body heat loss decreases with 4% each decade after the age of 20 years in healthy adults. The reduction in the ability to lose heat with ageing is for the largest part explained by the lower overall sweat rate in older adults, as evaporative heat loss is the strongest avenue of heat loss from the human body (55, 58). To the authors knowledge, no studies have investigated the age-related physiological decline between males and females in their ability to lose heat. However, it is known that females sweat less than males, and older females sweat less than younger females, indicating that the ability of older females to lose heat from the body is the lowest (62, 182). Heat puts considerable stress on the cardiovascular system, especially in older individuals who rely on a greater percentage of their maximum heart rate to increase cardiac output during whole-body heat stress than young adults, indicating greater cardiovascular strain (183). Not surprisingly, one of the main causes of heat-related mortality is related to a cardiovascular disorder (72). Cardiovascular strain is reportedly higher in females, potentially explaining their higher mortality risk in the heat (62, 184).

Furthermore, the behaviour of older males and females may also influence the higher risk for mortality in the heat. It has been reported, that older adults are less willing to use adaptive cooling strategies, potentially due to reduced sensitivity to thermal comfort, lack of social support or not wanting to be seen as 'old' and 'vulnerable' (185). Some studies suggest women initiate thermal behaviour to cool down earlier and use it to a greater extent than males (186, 187). However, these studies are conducted with young subjects and it is not known if this difference still persists in older adults. Van Steen et al. (2019) stated that females often outlive their male partners and therefore live alone, which has been reported as a contributing factor as physical and social isolation is highly correlated to heat-related mortality. It was also reported that females tend to be less active in general, but more active in the household (188). Continuing these activities during heat waves while being less physically fit puts females more at risk for overheating and cardiovascular strain than males (156). Furthermore, it was mentioned that females often have a lower income which is associated with lower quality housing and often no air conditioning; resulting in higher indoor temperatures (156). In the Netherlands housing quality is generally of a high standard and the houses are well insulated (189). Higher insulation may hamper heat removal during the summer, thus increasing indoor heat stress. However, a previous study showed that insulation only plays a minor role in the risk of overheating and when ventilated proper insulation even lowers the severity and risk of overheating (190). Furthermore, the ownership of air conditioning units is not that common in the Netherlands (189, 191). Therefore, it seems unlikely that a lower income of females will explain the sex differences in heat-related mortality in the Netherlands when considering housing quality and use of air conditioning.

More research is needed to determine these sex differences in heat-related mortality from both a physiological and behavioural perspective. The limited number of physiological studies with female participants may be contributing to our poor understanding of their response to the heat. A better understanding of these differences will allow for better targeted heat policies for both males and females and potentially lower heat-related morbidity and mortality across the general population. For example, in 2007 a heat health warning system (HHWS) was developed in the Netherlands which is activated if there is a high chance of five consecutive days with an ambient temperature exceeding 27°C (192, 193). More attention for females in the HHWS could be a next step at decreasing the negative effects of heat for females.In the cold a significant higher effect on mortality was found for the age groups 65-80 and ≥80 years, but no sex differences were observed. Cold-related mortality in older adults has mostly a cardiovascular, respiratory, and cerebrovascular origin (149). The observed absence of any sex differences in the cold is in line with a previous study done in the USA (165). However, other studies have reported a higher male or mortality in females in the cold (157, 159, 163, 164). Sex differences in the cold seem to be less prominent than in the heat, as there is no consensus in outcome of different studies. Potentially this is the case as the physiological disadvantage of males, e.g. the lower body fat content, can easily be compensated with thermoregulatory behaviours such as adding an extra layer of clothing (154). A previous study showed that males wear 0.14 clo more than females, suggesting this may indeed be the case (194). Furthermore, adaptive behaviour to the cold may differ between countries and therefore result in different outcomes in mortality. One specific difference in adaptive behaviour to the cold between regions is the wearing of gloves, hats and scarfs, which is reported to be less frequent in the southern regions of Europe (194). Another explanation for the lack of consistency in sex differences in cold-related mortality between studies is the level of income of the elderly population in a country. People with higher incomes can afford better insulated houses and energy to warm their houses in winter, which reduces their exposure to the cold compared to people with lower incomes (195). However, not much is known about these potential behavioural differences between countries and future research should focus on this, which could be used to adapt policies regarding behaviour in the cold.

4.5.1. Limitations

As our analyses concern all-cause mortality only, this limits our interpretation of the specific causes of cold- and heat-related mortality. Furthermore, the temperature data of the five weather stations in the Netherlands were averaged and considered to be indicative for the weather conditions in the Netherlands. Ambient temperature at the location where a person passed away can differ from the mean ambient temperature. However, this difference is considered to be minimal in a small country like the Netherlands with a mean standard deviation of 0.7°C between weather stations. In the current study only mean ambient temperature is used to represent the thermal environment and no other parameters like humidity and solar radiation. A previous study showed no correlation between mortality and humidity, indicating that potentially humidity had limited influence in the current study as well (196). However, future studies should focus more in depth what the effect is of different environmental parameters, like humidity and solar radiation, on the higher mortality in females, preferably using data at a regional or local level. Moreover, no correction was made for the mean age of the males and females within each age group. However, as shown in table 1, mean age within each age group is almost similar. Therefore, it is assumed to have no effect on the reported results.

4.5.2. Conclusion

Mortality in the Netherlands represents the typical V- or hockey-stick shaped curve with a higher daily mortality in the cold and heat than at milder temperatures in both males and females, especially in the age group ≥80 years. Heat-related mortality in the Netherlands was higher in females than in males, especially in the oldest age group (≥80 years) under extreme heat, whilst in the cold no sex differences were found. The underlying cause may be of physiological or behavioural nature, but more research is necessary.

Chapter 5

Long term adaptation to heat stress: shifts in the minimum mortality temperature in the Netherlands

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5.1. ABSTRACT

It is essentially unknown how humans adapt or will adapt to heat stress caused by climate change over a long-term interval. A possible indicator of adaptation may be the Minimum Mortality Temperature (MMT), which is defined as the mean daily temperature at which the lowest mortality occurs. Another possible indicator may be the heat sensitivity, i.e. the percentage change in mortality per 1°C above the MMT threshold, or heat attributable fraction (AF), i.e. the percentage relative excess mortality above MMT. We estimated MMT and heat sensitivity/AF over a period of 23 years for older adults (> 65 years) in the Netherlands using three commonly used methods. These methods are Segmented Poisson regression (SEG), constrained segmented distributed lag models (CSDL) and distributed-lag non-linear models (DLNM). The mean ambient temperature increased by 0.03°C/yr over the 23 year period. The calculated mean MMT over the 23-year period differed considerably between methods (16.4 ± 1.2°C (SE) (SEG), 18.9 ± 0.5°C (CSDL) and 15.3 ± 0.4°C DLNM). MMT increased during the observed period according to CSDL (0.11 ± 0.05°C/yr) and DLNM (0.15 ± 0.02°C/yr), but not with SEG. The heat sensitivity, however, decreased for the latter method (0.06 %/°C/yr) and did not change for CSDL. Heat AF was calculated for the DLNM method and decreased with 0.07 %/yr. Based on these results we conclude that the susceptibility of humans to heat decreases over time, regardless which method was used, because human adaptation is shown by either an increase in MMT (CSDL and DLNM) or a decrease in heat sensitivity for unchanged MMT (SEG). Future studies should focus on what factors (e.g., physiological, behavioural, technological or infrastructural adaptations) influence human adaptation the most, so it can be promoted through adaptation policies. Furthermore, future studies should keep in mind that the employed method influences the calculated MMT, which hampers comparability between studies.

5.2. INTRODUCTION

Humans possess a great capacity to acclimatize to heat (197). Over a period of approximately 10 days, cardiovascular, thermoregulatory and fluid control mechanisms are optimized so that heat strain has a reduced effect on human well-being and performance. These acute adaptations are well documented (28, 197), but adaptations to long term exposure (i.e., several years) are essentially unknown. This is problematic for accurate estimations of future morbidity and mortality in the face of climate change, with numerous scientific papers making a disclaimer for the unknown effects of the 'human adaptation' (198). When adaptation to heat is assumed, it has a considerable impact on predicted mortality and associated societal costs (199).

Heat related excess mortality is mainly observed in elderly subjects (200). Older adults (>65 years) are most at risk for temperature related mortality due to intrinsic changes in the thermoregulatory system, like a reduced sweat response and thirst sensation (201, 202). In addition, older adults are often less physically fit and have more illnesses and disabilities what makes them also more susceptible to heat-related morbidity and mortality (203). However, older adults are able to acclimatize to the heat (204, 205) when a sufficient number of days for adaptation is allowed (182). Furthermore, they may be more resilient to heat in hot cities than in colder cities (152). This increased resilience may be due to better housing, behavioural adaptations, increased use of air conditioners (191), improved awareness of heat impact due to public campaigns, but also due physiological adaptations of the human body to the heat.

Mortality data, especially in the older population, often exhibit a U- or V-shaped relationship with temperature (206), with the number of deaths increasing for temperatures below or above the so-called minimum mortality temperature (MMT). MMT is the mean daily temperature at which the lowest mortality occurs and quantifies the threshold between the cold and heat mortality slope. The term MMT was first used to illustrate the considerable differences in the temperature-mortality relationship in the United States (207): MMT for Boston was 21°C and 27°C for Miami. Cities show higher MMT values when located closer to the equator (208). This is observed for European cities (200), but also within countries. Tobias et al. (209), for instance, showed that hotter cities have a higher MMT in Spain.

Recent studies have proposed the use of the MMT as a potential indicator of human long-term adaptation to heat in case the MMT shifts to a higher temperature (210-212). If humans become less susceptible to heat, an increase in MMT can be expected over time, similar to higher MMT values in warmer cities due to geographic differences. Todd and Valleron (211) found an increase in MMT from 17.5°C in 1968-1981 to 17.8°C in

1982-1995 and 18.2°C in 1996-2009 in France. An increase in ambient temperature of 1.6°C over these years was accompanied by an increase in MMT of 0.8°C. For comparison: a temperature difference of 1.6°C between geographical areas was accompanied by a 1.1°C increase in MMT.

There are several approaches to calculate MMT from temperature-mortality time-series data and different methods have been used in the studies mentioned above. One simple statistical model predicting the logarithm of the death counts by actual temperature is the segmented Poisson regression model (SEG) providing estimates of the breakpoint (MMT) as well as of the negative temperature slope in the cold and positive slope in the heat, while accounting for covariates, e.g. day of week (213-215). Only focusing on the temperature influence on the same day, SEG neglects the time series structure, and especially does not consider lagged effects of temperature on mortality. However, it is easily applicable to separate one-year periods allowing for assessing the development of MMT over the whole observation period, as well as of heat and cold sensitivity from the respective slopes. The constrained-segmented distributed lag model (CSDL) also includes MMT as estimated parameter, but extends the simple V-shape model by considering non-linear lagged effects as well as long-term and seasonal trends in the time series (216, 217). By additionally relaxing the linear V-shape assumption, so-called distributed lag nonlinear models (DLNM) allow to fit more flexible temperature-mortality relationships to such time series data (218, 219). DLNM requires an extra step applying a search algorithm for finding the MMT (209). Both the CSDL and DLNM models usually rely on longer observation periods covering at least 10 – 20 years. Thus, in order to assess the development of MMT over time, recent studies fitted the data to the observations from non-overlapping (211, 220, 221) or partly overlapping (212, 222) sub-periods.

It is unknown if the variation in MMT is due to human adaptation or due to the methods used to calculate MMT as outlined above. Therefore, the aim of the current study was two-fold: we investigated changes in MMT in the Netherlands over a period of 23 years, from 1995 to 2017, for older adults (> 65 years), whilst comparing the three previously mentioned models (SEG, CSDL, DLNM).

5.3. METHODS

5.3.1. Database

The daily number of deaths and population size in the Netherlands, obtained from Statistics Netherlands (CBS), and temperature data, obtained from the Royal Netherlands Meteorological Institute (KNMI) from 1 January 1995 to 31 December 2017 were used for the calculations in this study. Only mortality in the age group of 65 years and older was processed, because this group is reportedly the most vulnerable to extreme ambient temperatures (203).

Hourly ambient temperature was obtained from five weather stations representative for the Netherlands: Station De Bilt (in the centre of the Netherlands,), Station Eelde (rural area, farmland, northern part of the Netherlands), Maastricht (average sized city, southern part of the Netherlands), Rotterdam (large city near the coast, western part of the Netherlands) and Schiphol airport (industrial area, amid densely populated areas, western part of the Netherlands). Daily temperature used in this study was obtained by averaging the hourly values over the five weather stations and time.

5.3.2. Model calculations

Calculations were performed using R version 3.6.1 (223). For the entire time series, a segmented Poisson regression model (SEG) allowing for over dispersion (224) was fitted to daily mortality with daily mean temperature as predictor and day-of-week as only covariate using the R package *segmented* (213-215). Estimates and SE were provided for MMT and for the cold and heat slope parameters. Relative risks (RR) with mortality at MMT as reference were calculated by exponentiation of the slope parameters multiplied with the difference of MMT to temperature. Sensitivities to cold and heat calculated by exponentiation of the slope estimates were expressed as percentage change per degree decrease or increase in temperature from MMT, respectively.

Similarly, we also obtained MMT and sensitivities to heat and cold by fitting constrained segmented distributed lag (CSDL) models using the package *modTempEff* (216, 217) controlling for the day-of-week, while considering lag temperature effects and adjusting for annual and seasonal trends with spline functions as suggested by the software manual (216).

Distributed-lag non-linear models (DLNM) were fitted using the *dlnm* package (218), also including day-of-week covariate while considering lag temperature effects up to 25 days and adjusting for long-term and seasonal trends with spline functions using eight degrees-of-freedom per year. MMT with SE was estimated by a search algorithm over the fitted response function (209). The sensitivities to heat and cold were calculated using the attributable fraction (AF), expressed as percentage relative excess mortality integrated over the lag periods and temperatures above and below MMT, respectively (174).

5.3.3. Shift in MMT and sensitivity to heat and cold

The shift in MMT over time in the SEG method was calculated by fitting the SEG model for every year separately. For CSDL and DLNM, the models were repeatedly fitted to reduced series from a sliding 15-year window, which was shifted by 1-year increments throughout the entire observation period.

A shift of MMT and heat and cold sensitivities (AF for DLNM) was assessed by performing linear regression analyses for changes in the parameters weighted by their inversed SE over time, while statistical significance was assumed for p-values < 0.05.

5.4. RESULTS

The average number of deaths in the Netherlands over the investigated 23-year time span was 382 ± 40 (SE) individuals per day. The mean daily temperature in the Netherlands was 10.5 ± 6.3°C . The mean temperature increase over the observed period was 0.03°C/yr. The number of people over 65 years increased from 2.0 million to 3.2 million between 1995 and 2017, but their mean age was stable at 74.5 ± 0.1 years over the investigated period (225).

Figure 1 shows the RR of mortality at different daily mean temperatures over the entire 23 year period according to the three different methods. The SEG and CSDL methods assume a linear relation and, therefore, have a V-shaped estimation of the temperature-mortality curve. The DLNM method assumes a nonlinear relation and, therefore, has a more U-shaped curve. The mean calculated MMT, and cold and heat sensitivity/AF are shown in table 1. Large differences are shown for the calculated MMT between methods with values between 15.3 ± 0.4°C for the DLNM method and 18.9 ± 0.5°C for the CSDL method. Cold sensitivity was similar with 1.3 ± 0.2% and 1.3 ± 0.3% for respectively the CSDL and SEG methods, but a large difference was found for the heat sensitivity with 5.6 ± 0.6% for the CSDL method and 1.5 ± 0.8% for the SEG method. The AF to the cold calculated with the DLNM method was higher than the AF to the heat, with respectively 5.0 ± 0.3% and 1.1 ± 0.2%.

Figure 2 shows the calculated MMT per year for the SEG method and with a sliding 15-year window for the CSDL and DLNM methods. Cold and heat sensitivity are reported for the SEG and CSDL methods and cold and heat AF for the DLNM method. A significant increase in MMT of 0.11 ± 0.05°C and 0.15 ± 0.02°C per year was observed for the CSDL ($p < 0.001$) and DLNM ($p < 0.05$) methods, respectively. However, no significant increase in MMT was found with the SEG method ($p = 0.96$). Cold sensitivity did not change over time in both the CSDL ($p = 0.57$) and the SEG methods ($p = 0.69$). Heat sensitivity did not change significantly in the CSDL method ($p = 0.12$), but did decrease significantly with the SEG method ($p = 0.01$) with 0.06 %/°C/yr. No significant difference in cold AF is shown ($p = 0.511$), however there was a significant decrease of 0.07 %/yr in heat AF ($p < 0.001$).

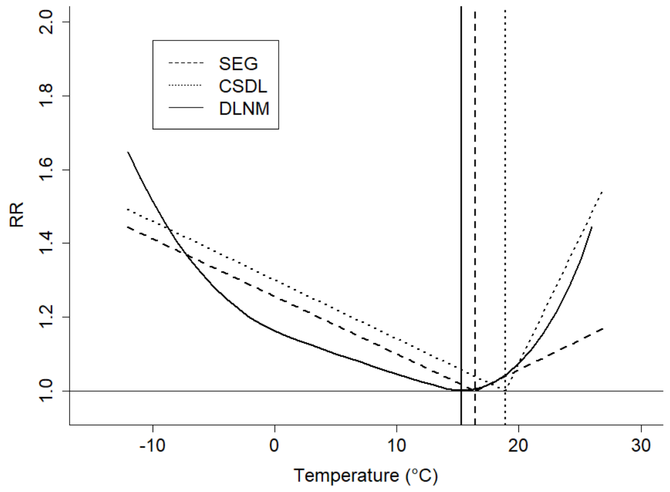


Figure 1. Temperature related to the relative risk (RR) for mortality of older adults (>65 years) for three different methods: Segmented Poisson regression (SEG), constrained segmented distributed lag models (CSDL) and distributed-lag non-linear models (DLNM), during the 23-year-period from 1 January 1995 to 31 December 2017 in the Netherlands. The minimum mortality temperature (MMT) estimated by the three different methods is shown with the vertical lines. The slopes of the lines represent the cold/heat sensitivity of the SEG and CSDL method, whereas the cold/heat attributable fraction (AF) of the DLNM method is determined as relative excess mortality integrated over the temperatures above and below MMT, respectively.

Table 1. Mean Minimum Mortality Temperature (MMT) (Mean ± SD), cold and heat sensitivity (SEG and CSDL models) and attributable fraction (AF) (DLNM model) (%) calculated for the 23-year-period from 1 January 1995 to 31 December 2017 in the Netherlands with the three different methods: Segmented Poisson regression, (SEG), constrained segmented distributed lag (CSDL) model and distributed-lag non-linear Poisson regression models (DLNM).

Method	MMT (°C)	Cold sensitivity (%/°C) / AF (%)	Heat sensitivity (%/°C) AF (%)
SEG	16.4 ± 1.2	1.3 ± 0.3[a]	1.5 ± 0.8[a]
CSDL	18.9 ± 0.5	1.3 ± 0.2[a]	5.6 ± 0.6[a]
DLNM	15.3 ± 0.4	5.0 ± 0.3[b]	1.1 ± 0.2[b]

[a] Sensitivity
[b] AF

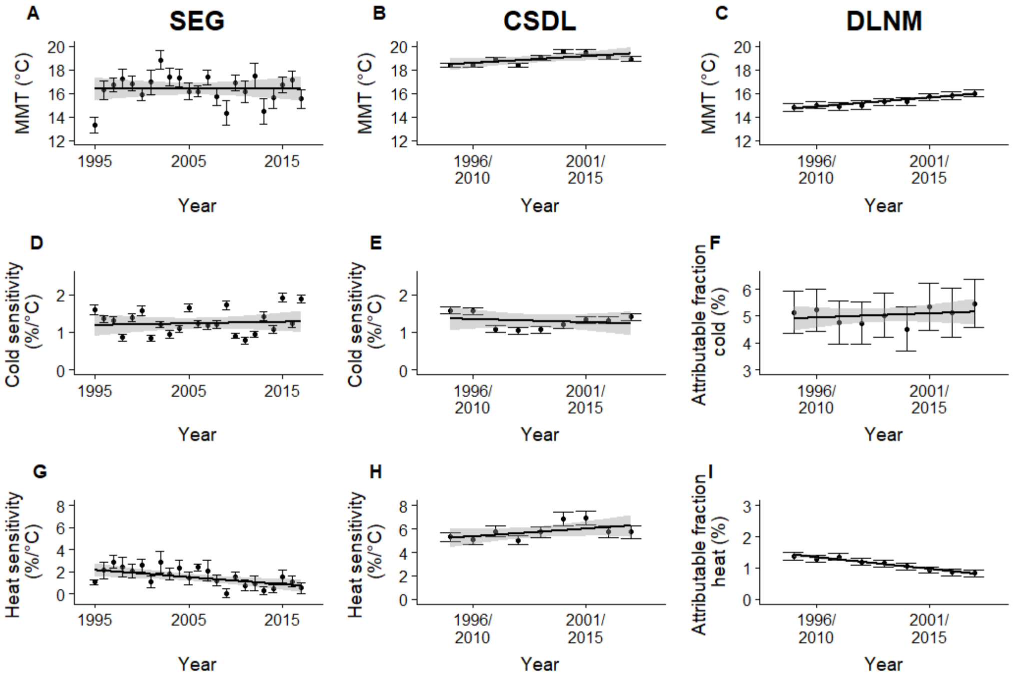


Figure 2. Changes in minimum mortality temperature (MMT) (A,B,C), cold sensitivity/Attributable Fraction (AF) (D,E,F) and heat sensitivity/AF (G,H,I) with standard errors and grey shaded 95% confidence bands estimated by three different methods: Segmented Poisson regression (SEG) (left panel), constrained segmented distributed lag model (CSDL) (middle panel) and distributed-lag non-linear Poisson regression models (DLNM) (right panel) of daily death counts for older adults (>65 years) related to daily mean temperature for the 23-year-period from 1 January 1995 to 31 December 2017 in the Netherlands.

5.5. DISCUSSION

The aim of the current study was to investigate the change in MMT, and cold and heat sensitivity/AF over a 23-year period for older adults (> 65 years) in the Netherlands using three different methods (SEG, CSDL, DLNM). Furthermore, the differences between the three methods were also analysed to investigate the influence of the employed method on the results.

The calculated mean MMT and heat sensitivity over the 23-year period differed considerably between methods. The CSDL method resulted in the highest MMT (18.9 ± 0.45°C) and heat sensitivity (5.6 ± 0.6%). The high heat sensitivity is a result of the higher MMT, as only days with a higher temperature than the MMT are included in the calculation of the heat sensitivity. In other words, the data is refined to the steepest part of the mortality curve (Fig. 1) resulting in a high heat sensitivity. The SEG method has a lower MMT (16.4 ± 1.2°C) and thus mortality data is included of more moderate temperatures above this low MMT threshold. The MMT calculated with the DLNM method was the lowest of all three methods with 15.3 ± 0.4°C. The cold AF is higher than the heat AF with 5.0 ± 0.3% and 1.1 ± 0.2% respectively, which can be explained with the fact that the average daily temperature in the Netherlands (10.5 ± 6.3°C) is below MMT and thus cold days are more prominent in the Netherlands. The differences in calculated MMT between methods are most likely due to the way the MMT is calculated in the models. Both the CSDL and DLNM method control for the day-of-week, annual and seasonal trends and consider lag temperature, while this is not the case in the SEG method. In addition, the DLNM method uses a non-linear approach, while both the SEG and CSDL method are linear. These results show that the used method has a large effect on the calculated MMT and the accompanying cold and heat sensitivity/AF. Comparability between studies employing different methods is therefore hampered.

The results of all three methods indicate that the susceptibility to heat in the Netherlands is declining over time. Two of the three methods (DLNM and CSDL) show an increase in MMT for adults over 65 years over the 23-year period (see figure 2A, B, C). The SEG method does not show an increase in MMT, but does show a decrease in heat sensitivity over time from about 2% to 1% per degree Celsius. This indicates that less people die at similar heat exposure suggesting a gradual adaptation to heat. The CSDL methods shows a slight increase in heat sensitivity, although not significant. This has to be considered in relation with the increasing MMT as the dataset for heat sensitivity will contain less moderate temperature days and increasingly more hot days. Therefore, it does not mean people are getting more susceptible to the heat based on the CSDL method. The same explanation accounts for the decrease in heat AF calculated with the DLNM method. As the MMT increases over time there are less days with a mean ambient temperature higher than the MMT and therefore less deaths are attributed to the heat. Cold sensitivity and AF do not change over the years for stable MMT (SEG) or for increasing MMT (CSDL and DLNM).

The observed increase of the MMT from 0.11 to 0.15°C/yr, accompanied with mean daily temperature increases of about 0.03°C/yr, is in line with previous studies (211, 212, 226). In France the observed shift in MMT was lower than in the current study with 0.025°C/yr for adults over 65 years old and an increase in summer temperature of 0.057°C/yr (211). In Sweden and Japan, the shift in MMT was more comparable with the current study with respectively 0.08°C /yr and about 0.12°C /yr for the whole population (212, 226). In Sweden the mean ambient temperature increased with 0.018°C /yr over the observed period and in the study of Chung et al. (226) the increase in mean ambient temperature was not reported. In the study of Todd and Valleron (211) Generalized Adaptive Models were used and in the studies of Åström et al. (212) and Chung et al. (226) the DLNM method was used similar to our study. The difference in applied methods may explain the smaller observed shift in MMT reported for France. However, all studies, including the current study for the Netherlands, suggest human adaptation to climate change.

These human adaptations to the increasing ambient temperatures can be attributed to multiple factors, such as physiological, behavioural, technological adaptations or changes in infrastructure (227). Repeated heat exposures lead to physiological adaptations in heart rate, body core temperature and sweat rate that slowly decay (228), and thus may lead to a more or less permanent state of heat acclimation (229). In line with this, it has been shown that mortality is considerably higher in the heat waves early in summer when compared to successive heat waves, probably partly due to heat acclimation in the subjects that survived the initial heat waves (230). Further, people born and raised in warm areas show reduced excess mortality in the heat when moved to relatively cold areas (231). Behavioural changes may occur because people become more aware of the impact of high ambient temperatures and raised awareness from the government. For example, since 2007 in the Netherlands, a heat health warning systems (HHWS) is activated if there is a high chance of five consecutive days with an ambient temperature exceeding 27°C (232). The aim of the HHWS is to warn people when extremely high temperatures are expected and to give behavioural recommendations (e.g., drink more, reduce physical activity) during these days. Technological and infrastructural changes over the years include improved building insulation that reduces heat loss in the cold and prevents heating of the house in hot periods. Air conditioning is an effective way of reducing heat strain. In the Netherlands the air conditioner demand already increased with about 24% between 2012 and 2017 according to the Japan Refrigeration and Air Conditioning Industry Association (191), probably contributing to the observed reduction in heat susceptibility over the years. A long term adaptation to climate change observed in endotherms is an increase in the body surface to mass ratio to enhance heat loss (233). In humans the body surface to mass ratio is higher in tropical than in cold areas (234). However, the body surface to mass ratio of the Dutch population shows a consistent linear decline over the investigated period (235), so no signs of climate change related morphological changes are observed.

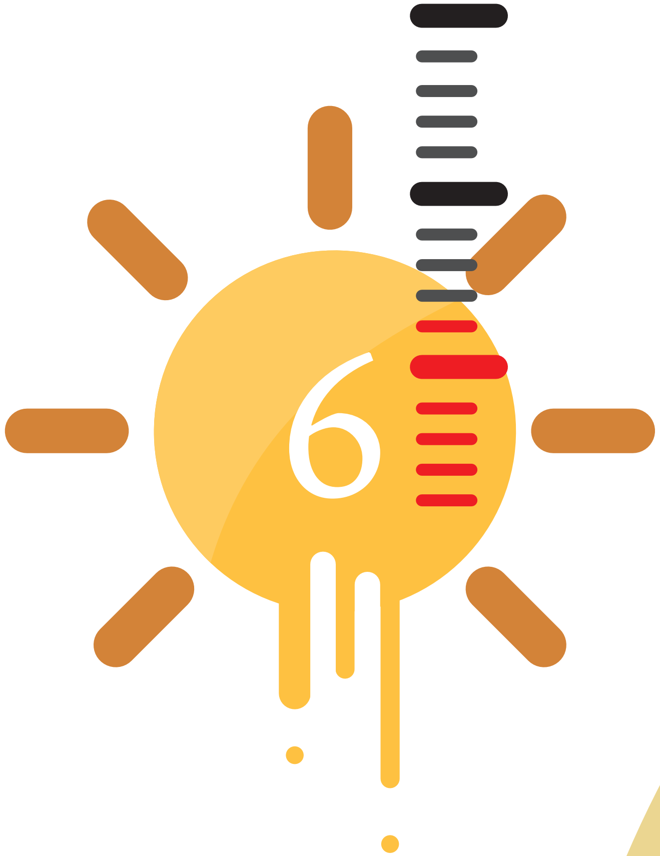
It has to be noted that the decreased susceptibility to heat over time may not only be related to climate change as suggested by Todd and Valleron (211). Arbuthnott et al. (236) showed that decreased heat susceptibility is a process that is not only visible in the last decades, but already started a century ago, when climate change was still negligible. Ten out of eleven included papers in their study found some evidence of decreasing susceptibility for heat over time. Cold susceptibility changes were negligible. It was argued that both planned adaptive measures, such as HHWS and improved buildings as well as adaptive behaviour, improved health and treatment of heat casualties could explain the changes. Still, climate change may accelerate the adaptations as Todd and Valleron (211) indicated.

Kinney (237) argued that human adaptation should be better quantified and included in methods used for predicting the effects of climate change on human survival. With ongoing climate change and associated adaptive processes, the temperature-mortality relationships on both sides of MMT may change, with the magnitude and direction of the change being uncertain. Future studies should focus on what particular factors, like the physiological, behavioural, technological or infrastructural changes mentioned before, are influencing the reduced susceptibility to the heat the most. Once the most effective factors are identified adaptation policies may be proposed accordingly.

In this study for the CSDL and DLNM method a 15-year sliding window was chosen, which covers quite an extensive part of the in total 23 years. Using sliding windows with fewer years resulted in larger volatility accompanied with a greater standard error, indicating a less precise MMT. However, previous studies like Aström et al (212) used a large sliding window as well of 30 years, although we are aware that they used a much larger total time period covering more than 100 years. Furthermore, data from the KNMI shows that an increase in ambient temperature is mostly present in the previous three decades, making it less relevant to use a dataset containing a longer time period than used in the current study (238).

5.5.1. Conclusion

The susceptibility of humans to the heat decreases over time in the Netherlands, regardless which method was used, as human adaptation was shown by either an increase in MMT (CSDL and DLNM) or a decrease in heat sensitivity for unchanged MMT (SEG). Underlying factors for the reduced heat susceptibility may be due to physiological, behavioural, technological or infrastructural adaptations. Future studies should focus on what factor influences the human adaptation the most, so it can be promoted through adaptation policies. Further, future studies should keep into mind that the employed method influences the calculated MMT and, therefore, reduces comparability between studies using different methods.



Chapter 6

Predicted and user perceived heat strain using the ClimApp mobile tool for individualized alert and advice

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6.1. ABSTRACT

Thermal models and indices integrated into a mobile application could provide relevant information regarding thermal stress and strain to the general public. The aim of the current paper is to validate such a mobile application, ClimApp, to the users need in the heat. ClimApp combines weather data with personal user data, thermal models and indices to estimate the thermal strain of the user. The output of ClimApp ranges from -4 to +4, where values below 0 indicate cold stress and values above 0 indicate heat strain. 134 participants filled in the required personal settings into the app, and indicated if the estimated thermal strain by ClimApp matched their thermal perception. 45 of the participants filled in a user satisfaction questionnaire. Results show that ClimApp is able to predict the heat strain of the user, but may underestimate perceived heat strain when ambient temperature increases. Furthermore, participants were positive about the user-friendliness of ClimApp, but did not think they would use ClimApp frequently and believed the information was irrelevant for them. This is quite remarkable as the number of heat illness cases are increasing and the negative effects of heat occur in all populations exposing themselves to the heat. There needs to be more focus on making people aware of the negative health risks of the heat. ClimApp could play a role as a tool to make heat warnings more accessible for everyone and make people aware of appropriate behaviour during periods with high ambient temperatures.

6.2. INTRODUCTION

Globally, emerging trends of increased duration, frequency and intensity of heat waves are being reported (147, 239, 240). Record high ambient temperatures are now more common and the most extreme temperatures are even more intense (241). In some climate regions the heat is already considered to be intolerable and has a severe impact on humans' daily life and health (242, 243). Heat limits the time people are able to be physically active and reduces work productivity, as more breaks are required to avoid health problems like dehydration, spasms and fatigue or even more serious illnesses such as heat stroke (242, 244). A study predicted that heat acclimatized people in Perth in 2070 will not be able to perform manual labour for 15-26 days a year due to the extreme heat, while currently it is only one day per five years (245). For unacclimatized individuals of low physical fitness and low body mass, performance decrement is probably greater, as these factors are shown to be most detrimental for working in the heat (19, 246). Furthermore, the advancing ageing population will see a rise in the number of heat related morbidity and mortality as people get older (39, 150).

Over the last decades more than one hundred heat stress indices have been developed to quantify heat stress and strain and reduce the health risks associated with high temperatures (11, 12). These indices vary significantly in their complexity and applicability (11). Simple indices are used more frequently as they are easier to understand for the general population. However these are often less accurate, omit important factors that affect the heat exchange between the body and the environment, and may underestimate the heat stress or strain perceived during high intensity exercise or outdoor manual labor (11, 247). This can lead to dangerous situations as potentially inappropriate measures may be taken due to over- or underestimation of heat stress or strain based on misuse or misinterpretation of these thermal indices. More complex indices and thermal models provide a better estimation of the heat stress or strain as these take into account more input parameters and individual variation. However, these indices and models may be difficult for the general public to interpret and use. To date, complex indices are mainly used in research (11). A solution to make these complex indices, models and international standards more accessible could be to integrate them into mobile applications. The user can fill in personal information as input to estimate the heat strain and receives output in the form of individualized advice to adapt behaviour to the current thermal environment. The input of personal information is essential for individualized advice as heat strain is dependent on factors such as activity level, clothing, age, sex, heat adaptation and weight (248-251). More heat is produced in the body when the activity level increases and the clothing insulation influences the amount of heat that can be lost via the skin (8). Age influences the heat dissipation as the thermoregulatory system of children is not yet fully developed and in older adults the function declines (39-41, 46). Furthermore, women have lower sweat rates and a higher heat storage than men, which mainly results in higher experienced heat strain at heavy heat loads (19, 62). Heat adaptation occurs after sufficient and repeated heat exposure and results in, amongst others, improved sweating response and a lower heat storage (19, 28). Weight influences the experienced heat strain as well, as individuals with a higher body mass can store more heat than individuals with a lower body mass (19).

A few mobile applications based on thermal indices are already developed, like the Hot Environmental Assessment Tool (252), the Occupational Safety and Health Administration – National Institute for Occupational Safety & Health (OSHA-NIOSH) Heat Safety Tool (253) and the Predicted Heat Strain mobile application (254). However, these mobile applications lack accuracy or user-friendliness due to the need to manually input weather information (252), weather information based only on ambient temperature and humidity or a tool too complicated for laymen with usability issues (253, 254). Furthermore, there is a chance the heat strain estimated by the thermal index does not coincide with the thermal perception of the user. This can be due to individual variation or parameters that are not included in the thermal index, but do influence thermal strain. Before these complex thermal indices integrated into mobile applications are provided to the general public, the outcome of the predicted thermal strain by the mobile application needs to be validated against the thermal perception of the user.

In the current paper, we aim to briefly describe the development of a new mobile application, ClimApp, which combines weather data with thermal models and indices, and user data to provide the user with individualized and timely advice on appropriate actions in thermally challenging environments and activities. Next, we aimed to validate the output of the app in the heat with the thermal perception of users and test the user-friendliness by a questionnaire.

6.3. METHODS

The methodology is separated into two distinct sections. The first section briefly describes the development of ClimApp and the second section of the study that was performed to validate the output and test the user-friendliness of ClimApp in the heat.

6.3.1. Development of ClimApp

ClimApp is developed by a group of experts in the field of thermal physiology, occupational, environmental and public health, computer science, ergonomics, thermal comfort and climate science from the Lund University, University of Copenhagen, Technical University of Denmark and the Vrije Universiteit Amsterdam. The mobile application aims to provide the user with a prediction of the thermal strain and advice on precautionary measures based on information about meteorological data, individual user characteristics and thermal models and indices. ClimApp provides information about thermal strain, and not thermal stress, as individual user characteristics are included in the output such as acclimatization status and metabolic rate. Projected users include outdoor workers and (the caregivers of) vulnerable groups, such as children and elderly. It can be used by employers of outdoor workers to decide how many breaks they should take and how much water they should drink in the heat, or by (the caregivers of) vulnerable people to estimate if cooling needs to be provided, to name some examples. The interface of ClimApp is shown in the appendix and the mobile application can be downloaded for iOS and Android. Below a brief description of the development of ClimApp is provided. A more elaborate and technical description can be found in Kingma, Steenhoff (255).

Meteorological data

Meteorological data are extracted and computed from the Open Weather Map API based on the user's GPS location (256). The data consists of air temperature (°C), wind speed at 2 and 10 meter high (m/s), humidity (%), cloud coverage (%) and solar radiation (W/m^2) for now and a forecast for the next 24 hours (with 3h time resolution).

Individual user characteristics

The user can choose to fill in their age, sex, height, weight and if they consider themselves to be heat acclimatized. Heat acclimatization is defined as being exposed to the same or more extreme hot conditions for at least one week prior to the assessment period. The mobile application user fills in the appropriate activity level, ranging from rest (sitting at ease) to severe (very intense occupational activity at fast maximum speed). Finally, the user supplies information about the clothing composition.

Thermal indices

Several heat balance models and thermal indices are used in ClimApp. For cold stress the required clothing insulation (IREQ) (257) and Wind Chill index (258) are used. As this paper focusses on the heat, the IREQ, Wind Chill index and the use of the mobile application regarding cold stress are not discussed. For heat stress and heat strain the Wet Bulb Globe Temperature (WBGT) (16) and Predicted Heat Strain (PHS) (18) are used. The WBGT together with the Heat Shield Risk Level (HRL) (259) are combined into the so-called ClimApp index .

WBGT is a heat stress index that represents the thermal load of an environment a person is exposed to (16). In ClimApp, the weather parameters (air temperature (°C), wind speed at 2 and 10 meter high (m/s), humidity (%), cloud coverage (%) and solar radiation (W/

m²)) derived from the Open Weather Map API are used to calculate the WBGT using the method of Liljegren, Carhart (14). In ISO 7243 reference values ($WBGT_{ref}$) are provided for five levels of metabolic rate and heat acclimatization status (16). As default, a long sleeve cotton shirt and cotton pants are assumed to be worn as work clothing in the heat. Otherwise the WBGT is corrected with a clothing adjustment value (CAV) to obtain a WBGT value ($WBGT_{eff}$) representative for the perceived heat stress with that type of clothing (Eq.1) (16).

$$WBGT_{eff} = WBGT + CAV\ [°C] \qquad \textbf{Eq.1}$$

The predicted thermal strain of the user in ClimApp, based on the WBGT and the Heat Shield Risk Level (HRL) in the heat, is shown as the ClimApp index (259). The ClimApp index ranges from -4 to +4, where values below 0 indicate cold strain and values above 0 indicate heat strain. In the heat, the HRL is used to determine the ClimApp index values by defining a ratio of the $WBGT_{eff}$ over the reference values of the WBGT ($WBGT_{ref}$) (Eq.2) (259). The HRL is categorized as not significant (HRL<0.8), low (0.8<HRL<1), moderate (1<HRL<1.2) and high risk (HRL>1.2). The $WBGT_{ref}$ is calculated separately for acclimatized (Eq.3) and unacclimatized (Eq.4) people with metabolic rate (M) in Watts.

$$HRL = \frac{WBGT_{eff}}{WBGT_{ref}} \qquad \textbf{Eq.2}$$

$$WBGT_{ref,acclimatized} = 56.7 - 11.5\log_{10}(M)[°C] \qquad \textbf{Eq.3}$$

$$WBGT_{ref,unacclimatized} = 59.9 - 14.1\log_{10}(M)[°C] \qquad \textbf{Eq.4}$$

The ClimApp index is calculated with the HRL as follows:

- ClimApp index < 1: no significant heat risk is expected.
    - HRL <0.8
    - *ClimApp index* = $\frac{HRL}{0.8}$
- 1 < ClimApp index < 2: the recommended alert limit is being approached and moderate heat strain can be expected.
- HRL between 0.8 - 1.0
    - *ClimApp index* = 1 + $\frac{HRL-0.8}{0.2}$
- 2 < ClimApp index < 3: the recommended alert limit is surpassed and high heat strain can be expected.
    - HRL between 1.0 -1.2
    - *ClimApp index* = 2 + $\frac{HRL-1.0}{0.2}$
- ClimApp index > 3: The recommended alert limit is surpassed by more than 20% and severe heat strain can be expected.
    - HRL > 1.2
    - *ClimApp index = 3 + (HRL - 1.2)*

Furthermore, the PHS is used to calculate the total amount of sweat loss and the duration until a rectal temperature of 38°C is reached. In the PHS the heat balance between the human body and the environment is calculated, based on weather condition, the activity level, clothing and heat acclimatization (18). Based on this information the maximum exposure time is advised in ClimApp and how much fluid intake would be sufficient to replace the fluid lost by sweating.

6.3.2. Validation of ClimApp

Ethical approval

Participants gave consent in ClimApp to use their data for research purposes. For participants under the age of 18 years parents or caregivers gave written consent.

Participants

For this study a heterogeneous group of participants were recruited to test the validity of ClimApp to have a wide variation of potential users. Participants were recruited from different places and sources in the Netherlands, such as via a summer camp in Leusden, The Netherlands, advertisements on social media and sport clubs, by email or asking acquaintances. Participants were excluded if they did not have access to a technical device to install ClimApp or were unable to understand the used technology in the mobile application.

Study procedure

An instruction sheet displaying all necessary steps and information on how to download and use ClimApp was sent to each participant by email. Additionally, a video incorporating these instructions was recorded and sent to participants for extra clarification. All participants were requested to follow all steps which consisted of installing the mobile application, allowing the application to use GPS and fill in personal settings such as age, height, weight, sex and if the users considered themselves to be heat acclimatized. After these initial steps the participants were free to upload data entries at any time or day of the week. These data entries were requested during the four weeks of August 2020. A data entry consisted of entering clothes worn at that moment and the activity level. Once this was filled in, ClimApp provided as output the expected thermal strain at that moment. Next, the participant was requested to enter if the perceived thermal strain was similar, lower or higher than the predicted heat strain by ClimApp. This deviation in thermal perception from the ClimApp index (TP_{dev}) ranges from -4 to +4 and is 0 if the ClimApp index was the same as the perceived thermal strain, higher than 0 if the participant felt warmer than the predicted thermal strain of ClimApp, and lower than 0 if the participant felt colder than the predicted thermal strain of ClimApp.

At the end of the study, all participants were requested to fill in a user satisfaction questionnaire about ClimApp. This questionnaire aimed to provide insight in the user experience of the application.

Statistical analysis

The data were analysed using RStudio 1.1.463 and Stata 16.0. The ClimApp index was validated using TP_{dev}. The output of ClimApp was considered to be an accurate representation of the heat strain if the TP_{dev} was 0, a good representation if TP_{dev} was between -0.5 and 0.5, a moderate representation if TP_{dev} was between -1.0 and 1.0, and a poor representation if TP_{dev} was < -1.0 or >1.0.

As the data were hierarchically structured, multilevel mixed-effects linear regression analysis was used to test statistically if the predicted heat strain of ClimApp coincides with the thermal perception of the user. The residuals were normally distributed and a model with a random intercept and slope for participant was fitted. The variable 'participant' was chosen to be included as level since the number of entries per participant differed. Three models were fitted with TP_{dev} as dependent variable and the empty model is shown (model A) for calculation of the explained variance. The independent variables were the $WBGT_{eff}$ (°C), age (per decade), sex and BMI (model B), the $WBGT_{eff}$ (°C) (model C) and the ClimApp index (model D). Explained variance (R^2) is calculated for model B, C and D using the following equation (eq.5) (260).

$$R^2 = 1 - \frac{\sigma^2}{\sigma_0^2} \qquad \textbf{Eq.5}$$

In equation 4 σ^2 is the level-one random error variance of the full model (i.e., model B, C or D) and σ_0^2 is the level-one random error variance of the empty model (i.e., model A).

The user satisfaction questionnaire about ClimApp was quantitatively analysed by calculating the percentage of participants providing a certain answer. The internal consistency between the statements of the questionnaire was calculated with Cronbach's alpha (261).

6.4. RESULTS

6.4.1. Validation of ClimApp

In total, 134 individuals (62 males, 72 females; characteristics presented as median (range); age: 25 (8 - 81) years, height: 177 (130-198) cm, weight: 67 (40-115) kg, BMI: 21.9 (13.7 – 32.6)) participated in this study. The total number of data entries were 1302 with a median number of eight per participant and a range of 1 to 46. Data were entered all over the Netherlands, and a few in Belgium and Germany, with a median (range) ambient temperature of 20.2°C (14.5 - 34.8°C), relative humidity of 72% (21 - 100%) and WBGT of 20.2°C (12.0 - 33.3°C).

Figure 1 shows the ClimApp Index (A), $WBGT_{ref}$ (°C) separately for acclimatized and unacclimatized individuals (B), and TP_{dev} (C) at $WBGT_{eff}$ (°C) measured in this study, as well as the TP_{dev} at the ClimApp index provided as output in this study (D). The ClimApp index shows values above zero only, indicating there was only heat strain and no cold stress during data collection. Table 1 shows the number of data entries representing a certain value or range of TP_{dev} filled in by the participants. 476 Data entries (36.6%) were 0, indicating the predicted heat strain by ClimApp was exactly the same as the thermal perception of the participants, which is considered as an accurate representation of the perceived heat strain. 354 data entries (27.2%) were between -0.5 and 0.5 (excluding 0), which is considered as a good representation of the perceived heat strain. 254 Data entries (19.5%) were between -1 and 1 (excluding -0.5 to 0.5), which is considered as a moderate representation of the perceived heat strain. 218 Data entries (16.7%) were higher than 1 or lower than -1, which is considered as a poor representation of the perceived heat strain.

Table 2 shows the results of the multilevel mixed-effects linear regression analysis for the relation between TP_{dev} with the $WBGT_{eff}$ separately (model B) and with age (per decade), sex and BMI (model C), and with the ClimApp index (model D). Results show a significant relation ($p < 0.001$) between TP_{dev} and the $WBGT_{eff}$, but not with age, sex and BMI. Equation 6 shows the relation between TP_{dev} and the $WBGT_{eff}$. At a $WBGT_{eff}$ of 13.5°C TP_{dev} exceeds 0 and increases with 0.08/°C, indicating thermal perception increasingly exceeds the predicted heat strain by ClimApp as $WBGT_{eff}$ gets higher. A significant relation ($p < 0.001$) is shown between TP_{dev} and the ClimApp index. Equation 7 shows that the deviation in thermal perception of the predicted heat strain by ClimApp increases once the ClimApp index is higher. The explained variance (r^2) of TP_{dev} by the $WBGT_{eff}$ and ClimApp index is low with respectively 0.17 and 0.11.

$$TP_{dev} = -0.93 + 0.07 * WBGT_{eff} \qquad \textbf{Eq.6}$$

$$TP_{dev} = -0.17 + 0.60 * ClimApp\ index \qquad \textbf{Eq.7}$$

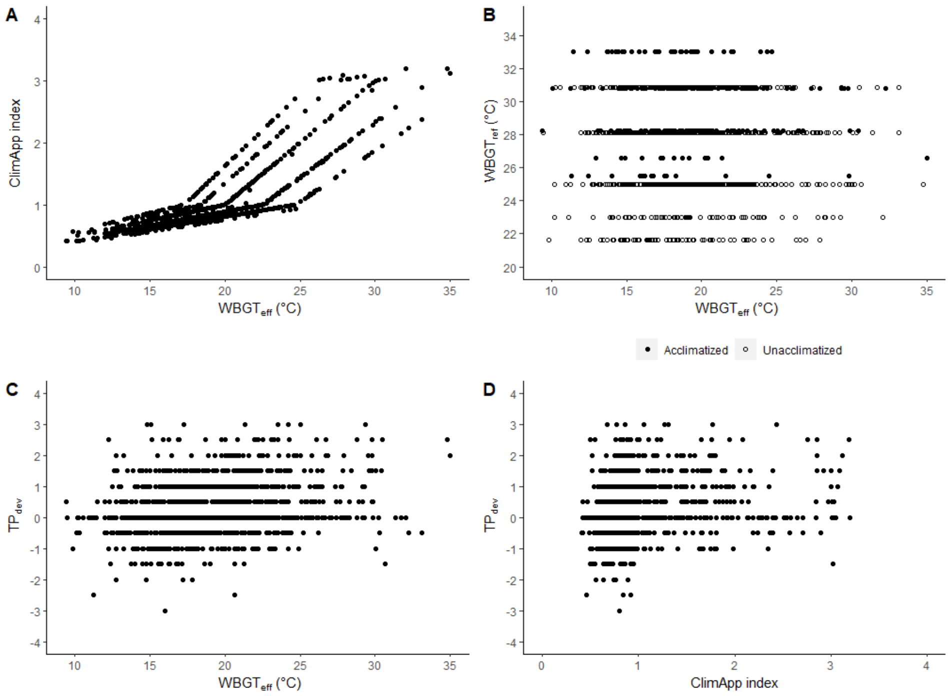


Figure 1. The ClimApp Index (A), reference values of the WBGT (WBGT$_{ref}$) (°C) separately for acclimatized and unacclimatized individuals (B), and the deviation in thermal perception from the ClimApp index (TP$_{dev}$) (C) at the effective Wet Bulb Globe Temperatures (WBGT$_{eff}$) (°C) measured in this study. D shows the TP$_{dev}$ at the ClimApp index provided as output in this study.

Table 1. Number of data entries representing a certain value or range of the deviation in thermal perception from the ClimApp index (TP$_{dev}$) filled in by the participants.

TP$_{dev}$	**Amount (percentage)**
> 1	191 (14.7%)
0.5 – 1	174 (13.3%)
0 – 0.5	183 (14.0%)
0	476 (36.6%)
-0.5 – 0	171 (13.1%)
-1 – -0.5	80 (6.1%)
< -1	27 (2.1%)

Table 2. Multilevel mixed-effects linear regression analysis for the relation between the deviation in thermal perception of the ClimApp index (TP$_{dev}$) filled in by the participants (Model A, empty model) with the effective Wet Bulb Globe Temperature (WBGT$_{eff}$), age (per decade), sex and BMI (model B), and separately with the WBGT$_{eff}$ (model C) and the ClimApp index (model D). The models are fitted with a random intercept and slope at the level of participant.

Model	**Dependent variable**	**Independent variable**	**Coefficient**	**95% CI^{a}**		**R^{2b}**
A	TP$_{dev}$	Intercept	0.42***	0.33	0.51	
		Random-effects parameters				
		Var (intercept)	0.18	0.12	0.28	
		Var (residual)	0.60	0.56	0.65	
B	TP$_{dev}$	WBGT$_{eff}$	0.07***	0.05	0.08	0.17
		Age	-0.05	-0.01	0.00	
		Sex	-0.02	-0.19	0.18	
		BMI	-0.01	-0.04	0.02	
		Intercept	-0.56*	-1.37	0.25	
		Random-effects parameters				
		Var (WBGT$_{eff}$)	0.00	0.00	0.01	
		Var (intercept)	1.05	0.53	2.08	
		Var (residual)	0.50	0.46	0.54	
C	TP$_{dev}$	WBGT$_{eff}$	0.07***	0.05	0.09	0.17
		Intercept	-0.93***	-1.23	-0.62	
		Random-effects parameters				
		Var (WBGT$_{eff}$)	0.00	0.00	0.01	
		Var (intercept)	1.07	0.54	2.10	
		Var (residual)	0.5	0.46	0.55	
D	TP$_{dev}$	ClimApp index	0.60***	0.45	0.74	0.11
		Intercept	-0.17*	-0.32	0.025	
		Random-effects parameters				
		Var (ClimApp index)	0.23	0.10	0.51	
		Var (intercept)	0.16	0.06	0.40	
		Var (residual)	0.54	0.49	0.58	

$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***} < 0.001$.
[a] Confidence interval
[b] Explained variance

6.4.2. User satisfaction questionnaire about ClimApp

Of the 134 participants, 45 (26 males, 19 females) filled in the user satisfaction questionnaire about ClimApp. Ages ranged between 16 and 40 and most people were in the age group 21-25 (18 participants) or 26-30 (12 participants). In the age groups 16 – 20, 31-35 and 36 – 40 there were respectively five, three and seven participants. Five participants mainly worked outside, three took care of an older adult and one took care of a child. The remaining participants' occupation were not specified in the questionnaire.

Figure 2 shows the answers of the participants on the user satisfaction questionnaire about ClimApp. The internal consistency of the statements in the questionnaire was good with an Cronbach's alpha of 0.87 (261). Most participants did not think they would use ClimApp frequently with 77.8% (strongly) disagreeing with the statement 'I think that I would like to use this mobile application frequently'. The majority of the participants believed the mobile application was not complex (S2: 64.5% (strongly) disagree), and thought the mobile application was easy to use (S3: 71.1% (strongly) agree) and they did not need the support of a technical person to be able to use the mobile application (S4: 80% (strongly) disagree). The various functions in the mobile application are well integrated with 37.8% (strongly) agreeing with question 5 and 37.8% did not agree/ disagree. Most participants did not think there was too much inconsistency in the mobile application (S6: 62.2% (strongly) agree). Part of the participants believed that most people could learn to use the mobile application quite easily (S7: 48.9% (strongly) agree), found the mobile application not cumbersome to use (S8: 68.9% (strongly) disagree) and did not need to learn a lot of things before to get going with the mobile application (S9: 73.3% (strongly) disagree). 35.6% of the participants thought ClimApp was useful, but 51.1% of the participants believed the information was irrelevant for them.

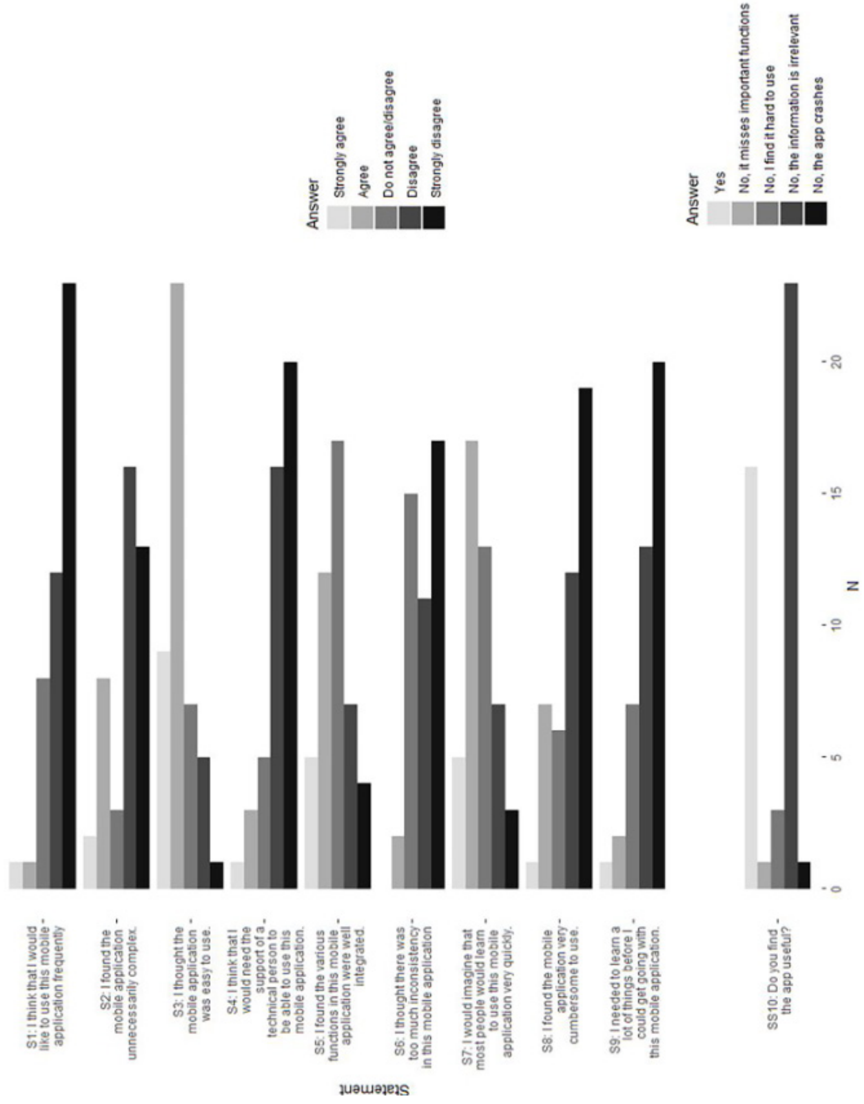


Figure 2. Number of participants providing a certain answer on the user satisfaction questionnaire about ClimApp

6.5. DISCUSSION

To our knowledge, this is the first study aimed to investigate the validity and user-friendliness of thermal models and indices incorporated in a mobile application to serve as a tool for the general public. It appears that the mobile application ClimApp is able to predict heat strain of the user rather well with 83.3% of the data entries of the participants ranked as a moderate, good or excellent representation of the perceived heat strain. However, the thermal perception increasingly exceeds the predicted heat strain by ClimApp as ambient temperature rises, although $WBGT_{eff}$ only represents 17% of the variance in TP_{dev}. The representation of the perceived heat strain becomes particularly poor at a $WBGT_{eff}$ higher than 28°C, since at that point TP_{dev} exceeds 1. These observations appear to be in line with another study where the WBGT was used as thermal index and resulted in a decrease in reliability once the heat strain risk condition and workload became more intense (262). It could be that thermal indices, such as in this case, predict the heat strain correctly, but that the thermal perception is higher. Since thermal perception plays an important role in thermal behaviour and acts as a warning mechanism of the human body, it could be that the experience of the heat is more intense than the actual heat strain (76). This way the individual is more inclined to change their behaviour before they experience the negative effects of the heat. If this is the case, it would make the use of a mobile application such as ClimApp, which has as a goal to warn about the risks of the heat, less valuable as the human body already does this itself. On the other hand, an individual could miss out on opportunities if activities are stopped too early without it being necessary from a health perspective. Therefore, it is important that the thermal perception accurately represents the experienced heat strain. However there are many cases of heat related disorders which could have been prevented if appropriate precautionary actions were taken. It could be that in some cases the thermoregulatory system of the human body does not function properly, which may be the case in vulnerable populations such as children and elderly. Other possibilities are that people do not adapt their behaviour well enough based on their thermal perception or are unable to adapt their behaviour. For example in occupations where it is difficult to self-pace such as in the military or fire brigade. It can also be that people are unaware of appropriate precautionary measures to reduce the perceived heat strain. In these cases, a mobile application as ClimApp can be of added value, as it advices the user on appropriate behavioural changes for the specific situation.

Furthermore, no relation was found between TP_{dev} and age, BMI and sex. A previous study showed that these factors do influence thermal sensitivity and comfort (263). Therefore, ClimApp seems to predict heat strain well for people of different age, BMI and sex. However, more older adults need to be included in a future study to confirm if ClimApp indeed provides an accurate prediction of heat strain for older adults, as only 10 of the 134 participants in this study were 65 years or older.

Overall the participants were positive about the user-friendliness of the mobile application and believed ClimApp was easy to learn and use. It has been shown before that the user-friendliness of a mobile application is critical for it to be used (264). Especially for a mobile application as ClimApp, it is important that it is easy to use and to interpret the outcome, as one of the main aims of ClimApp was to make thermal models and indices more accessible for the general public. However, most participants did not think they would use ClimApp frequently (77.8%) and believed the information was irrelevant for them (51.1%). This is surprising as previous research shows the number of heat illness cases are increasing and the negative effects of heat occur in all populations exposing themselves to the heat (265). A study investigating the public perception of the effect of heat on human health in the United States showed that people living in colder regions underestimate the effect of heat more than people living in areas with higher ambient temperatures (266). Meanwhile these people are more likely to experience the negative health effects of the heat as they are not acclimatized to the heat and are less familiar with adapting their behaviour. Since the Netherlands has a temperate marine climate with an average temperature of 10.5°C (175, 181) it is a relatively cold country and therefore it may be the case that Dutch citizens underestimate the effect of the heat as well. The same study showed older adults underestimate the effect of heat (266), which is worrying since they are most vulnerable for heat-related morbidity or mortality (150, 167). In the Netherlands since 2007 a heat health warning system is activated when a heat wave is expected, with the purpose of increasing awareness of the health risks of the heat to reduce heat related morbidity and mortality (192). However, a study looking into the effects of this heat health warning system showed that care organizations were not familiar with it and did not prioritize the heat as a risk factor (267). Furthermore, it has been reported that certain vulnerable groups, such as those who are socially isolated, have been overlooked in the heat health warning system (267). It appears there needs to be more focus on making people aware of the negative health effects of the heat and reach all groups of individuals. ClimApp could play a role as a tool to make heat warnings more accessible for everyone and make people aware of appropriate behaviour during heat strain.

6.5.1. Limitations and future directions

Although a large number of participants were included in this study, the larger part were healthy young (median age 25 years old) adults. Young and fit adults can be at high risk for, for example, occupational heat strain, since they can achieve larger metabolic rates than their older and less fit counterparts (19). However, in general young adults are not the most vulnerable for the effects of the heat. A future study should include more vulnerable people such as older adults, outdoor workers or people with certain diseases that makes them more vulnerable to the heat, to make sure a mobile applications, such as ClimApp, are applicable for these populations as well. Another limitation is the amount of people that filled in the user satisfaction questionnaire, which were only 34% of the participants. The young participants (<18 years) and older participants (>40 years old) were not included in the user satisfaction questionnaire, so the results are valid for adults aged 18-40 years only. Furthermore, only 5 out of the 45 participants who filled in the user satisfaction questionnaire were outdoor workers and only 3 caregivers of children or elderly, and therefore the participants perhaps believed the information was less relevant for them. It is recommended to include the young and older age groups and outdoor workers in future surveys since the appreciation of a mobile application may be dependent on age.

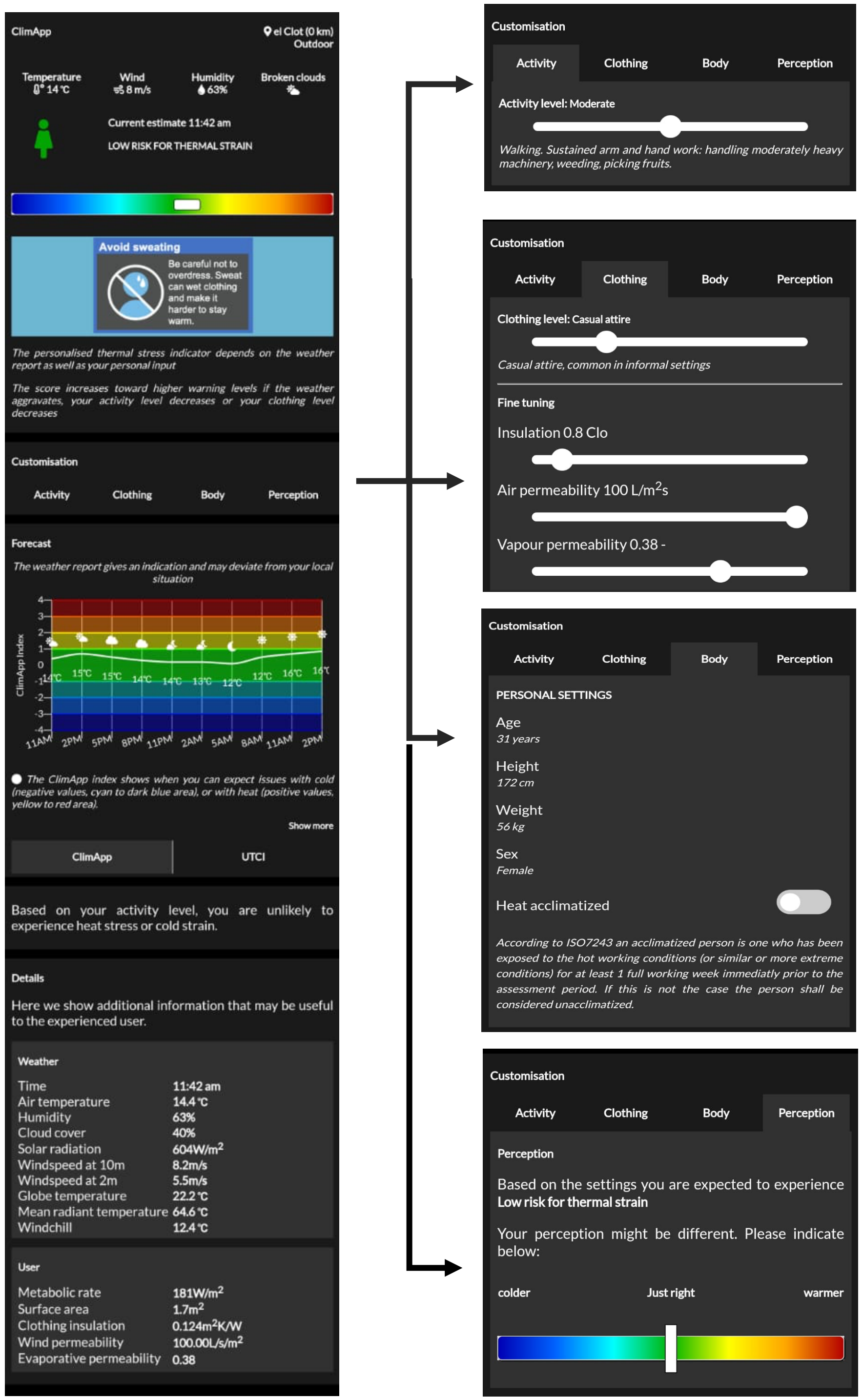
In this study we chose to measure deviation in thermal perception from the ClimApp score instead of absolute thermal perception, which may have influenced the outcome. However, in other fields, for example in wetness perception (268), methods rating the difference instead of absolute scores are often used as it is considered more reliable. Therefore, we believe the results in this study are valid.

ClimApp can be used in both the cold and the heat. However, the current study was only focused on validation in the heat. Therefore, a future study should focus on validating ClimApp in the cold as well.

6.5.2. Conclusion

The mobile application ClimApp seems to be a user-friendly and valid tool to predict heat strain of people of different age, BMI and sex. However, ClimApp may underestimate perceived heat strain when ambient temperature increases. Furthermore, more awareness needs to be created for the negative health effects of the heat, since most participants believed the information provided in ClimApp was irrelevant to them. ClimApp could play a role as a tool to make heat warnings more accessible for everyone and make people aware of appropriate behaviour during periods with high ambient temperatures.

APPENDIX - CLIMAPP INTERFACE



el Clot (0 km)
Outdoor

Temperature 14 °C
Wind 8 m/s
Humidity 63%
Broken clouds

Current estimate 11:42 am

LOW RISK FOR THERMAL STRAIN

Avoid sweating

Be careful not to overdress. Sweat can wet clothing and make it harder to stay warm.

The personalised thermal stress indicator depends on the weather report as well as your personal input

The score increases toward higher warning levels if the weather aggravates, your activity level decreases or your clothing level decreases

Forecast

The weather report gives an indication and may deviate from your local situation

● *The ClimApp index shows when you can expect issues with cold (negative values, cyan to dark blue area), or with heat (positive values, yellow to red area).*

Based on your activity level, you are unlikely to experience heat stress or cold strain.

Details

Here we show additional information that may be useful to the experienced user.

Weather

Time	11:42 am
Air temperature	14.4 °C
Humidity	63%
Cloud cover	40%
Solar radiation	604W/m^2
Windspeed at 10m	8.2m/s
Windspeed at 2m	5.5m/s
Globe temperature	22.2 °C
Mean radiant temperature	64.6 °C
Windchill	12.4 °C

User

Metabolic rate	181W/m^2
Surface area	1.7m^2
Clothing insulation	0.124m^{2}K/W
Wind permeability	100.00L/s/m^2
Evaporative permeability	0.38

Customisation – Activity

Activity level: Moderate

Walking. Sustained arm and hand work: handling moderately heavy machinery, weeding, picking fruits.

Customisation – Clothing

Clothing level: Casual attire

Casual attire, common in informal settings

Fine tuning

Insulation 0.8 Clo

Air permeability 100 L/m^{2}s

Vapour permeability 0.38 -

Customisation – Body

PERSONAL SETTINGS

Age
31 years

Height
172 cm

Weight
56 kg

Sex
Female

Heat acclimatized

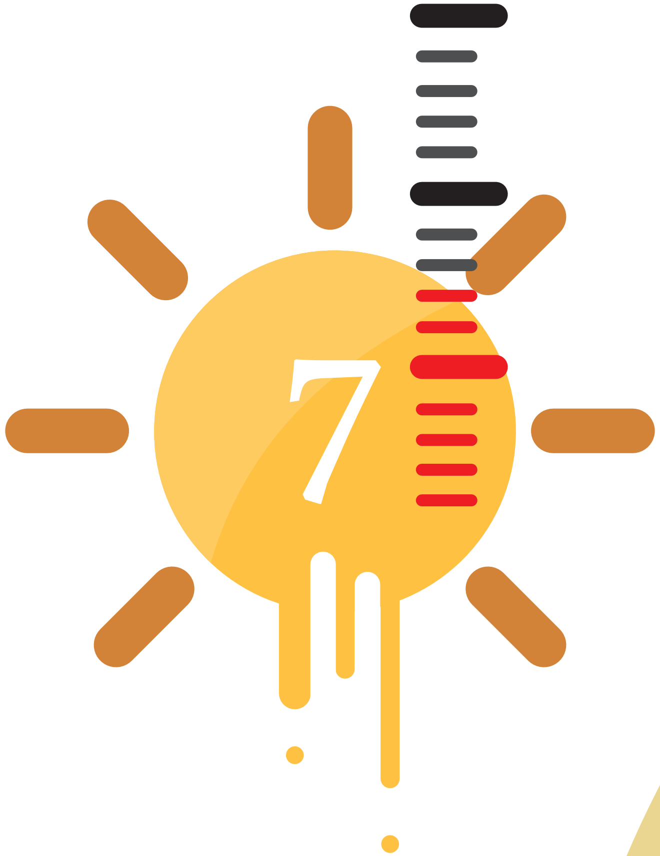
According to ISO7243 an acclimatized person is one who has been exposed to the hot working conditions (or similar or more extreme conditions) for at least 1 full working week immediatly prior to the assessment period. If this is not the case the person shall be considered unacclimatized.

Customisation – Perception

Perception

Based on the settings you are expected to experience **Low risk for thermal strain**

Your perception might be different. Please indicate below:



Chapter 7

Summarising discussion

Climate change is one of the major challenges to human health in the years to come (269). An increase in heat-related morbidity and mortality can be expected during heat waves. In order to reduce heat-related morbidity and mortality, combined expertise of medical experts, epidemiologists, health care specialists is required. Multidisciplinary research, including that of the studies presented in the current thesis, is necessary to create scientifically based information for heat policies for specific end users. A targeted approach in heat policies and advice regarding heat stress and heat strain is needed, as the level of vulnerability to heat-related morbidity and mortality is dependent on many physiological characteristics of the end user. These physiological characteristics are, for example, body morphology, heat adaptation status, aerobic fitness, age, sex and chronic health conditions.

Furthermore, current heat policies do not reach individuals who could benefit most from the advice; vulnerable groups, such as socially isolated people, are often missed (267). Tools, for example mobile applications, could be embedded in heat policies to reach a broader audience and provide relevant, individually focussed advice regarding the risks of the heat and precautionary measures. In this thesis the focus was on children, older adults, sex differences and how physiological characteristics combined with environmental parameters and thermal models and indices can be used to provide advice to the general public regarding heat stress and heat strain. In this last chapter a summary of the results is provided together with an evaluation in relation to the existing literature and suggestions for heat policies and future research.

7.1. CHILDREN

Young children (< 5 years) are largely dependent on their parents or care providers to be safe, healthy and comfortable. Children are vulnerable to high temperatures due to their behavioural dependability and their underdeveloped thermophysiological system (41, 46). Lately there is some discussion if children are indeed less effective in their thermoregulation. However, previous research has shown that significantly more children were brought into the emergency department in The Netherlands during days with high ambient temperatures compared to days with lower ambient temperatures, while this was not the case for adults (91).

Since the prevalence of dual-earner households is increasing, the number of children spending time in day-care centres has increased significantly (93). In day-care centres, care providers are responsible for the wellbeing of children, including their thermal comfort and safety. Knowledge about thermoregulation in children and appropriate precautionary measures to reduce the risk of heat strain in children are important for care providers working in day-care centres, especially since the number of hot days is increasing. Furthermore, care providers need to be able to estimate the thermal state of the children they are responsible for, as young children may have not developed the appropriate language skills to verbally communicate their thermal discomfort and their thermoneutral zone if different than that of adults (270). Since limited research is available on this topic, we investigated in *Chapter 2* the ability of the care providers to estimate the thermal state of the children and their knowledge on this topic. Skin temperature of four body locations was used as a proxy of the thermal state of the children. Results from this study show the care providers were unable to estimate the thermal state of the children correctly and many care providers had difficulties naming symptoms of heat illness. The care providers with less than 5 years work experience had a lower knowledge level of thermoregulation than care providers with more than 5 years work experience. Therefore, it is recommended to train care providers in thermal assessment, in particular novice care providers that may have less knowledge on this topic.

7.2. SEX

The WBGT is often used in occupational settings and during sport events to categorize the level of heat stress and take precautionary measures based on this categorization (11, 271). The reference values or critical WBGT for this categorization are environmental thresholds above which heat gain exceeds heat loss and body core temperature cannot be maintained at equilibrium. Once the environmental threshold is exceeded, the individual is in a state of uncompensable heat stress and, if the conditions remain the same, the thermoregulatory system cannot maintain a stable body core temperature. In ISO 7243, it is advised to reduce the heat stress or heat strain with appropriate measures, once the reference values of the WBGT are exceeded (16). These reference values are dependent on physiological characteristics and in ISO 7243 only acclimation status is taken into account (16). However, in *Chapter 3* we show that these environmental thresholds are also dependent on sex, as the critical WBGT for unacclimated women is lower than for unacclimated men when exercising at the same absolute intensity. Based on these results women seem to be more prone to the negative health effects of the heat. This is in line with previous research reporting greater increases in core temperature in women when working or exercising on similar intensities, most likely due to hormones, lower body mass and aerobic fitness (19, 63, 272). Therefore, separate reference values for men and women should be considered for the WBGT, or body mass and aerobic fitness should be included in ISO 7243. Especially since we show in *Chapter 4* that heat-related mortality in the Netherlands is higher amongst women than men, even after correcting for the larger population of older women. Temperature-related mortality occurs mainly in older adults, especially over 80 years old, and to a smaller extent in the age group 65-80 years old. In the age group over 80 years old the data indicated clear sex difference in heat-related mortality, with more women dying in periods of high ambient temperatures. Underlying causes may be of physiological or behavioural nature, but no definite cause could be provided based on existing research. The limited number of physiological studies with female participants may be contributing to our poor understanding of their response to the heat. A better understanding of these differences will allow for better targeted heat policies for both men and women and potentially lower heat-related morbidity and mortality across the general population.

7.3. OLDER ADULTS

Humans become more prone to the negative health effects of the heat with increasing age, mainly due to a reduction in the thermoregulatory function and lower aerobic fitness (40, 59, 272). The decline in thermoregulatory function occurs progressively. A study showed that already above the age of 20 years whole-body heat loss decreases with 4% every decade and becomes perceptible above the age of 40 years (57). As a result, the thermoneutral zone of elderly in narrower than that of adults (270). As previously mentioned and described in *Chapter 4* temperature-related mortality is age dependent with higher mortality rates in people older than 65 years. Next to a reduced functionality of the thermoregulatory system and a lower aerobic fitness behaviour plays a major role in the increased vulnerability of older adults. Research has shown that older adults are less willing to use adaptive cooling strategies, potentially due to reduced sensitivity to thermal comfort, lack of social support or not wanting to be seen as 'old' and 'vulnerable' (185). However, the study described in *Chapter 5* shows that older adults are able to adapt to the increasing ambient temperatures over the last few decades in the Netherlands. In this study the Minimum Mortality Temperature (MMT) and heat sensitivity/attributable fraction (AF) are used as proxies to investigate human adaptation to climate change. The MMT is defined as the mean daily temperature at which the lowest mortality occurs, heat sensitivity as the percentage change in mortality per 1°C above the MMT threshold, and heat AF as the percentage relative excess mortality above MMT. We determined MMT and heat sensitivity/AF over a period of 23 years, while mean ambient temperature increased by 0.03°C per year in the Netherlands, using three commonly used methods. Large differences were found in the calculated MMT between these three used methods, reducing comparability between studies using different methods. Results from all three methods show either an increase in MMT or a decrease in heat sensitivity for unchanged MMT, which indicates the susceptibility of humans to heat decreases over time. However, it is currently unknown if this reduced susceptibility to the heat is due to physiological, behavioural, technological or infrastructural adaptations. Once there is more knowledge about the underlying causes, heat policies could promote these methods for future implementation.

7.4. TOOLS TO REDUCE HEAT STRESS AND HEAT STRAIN

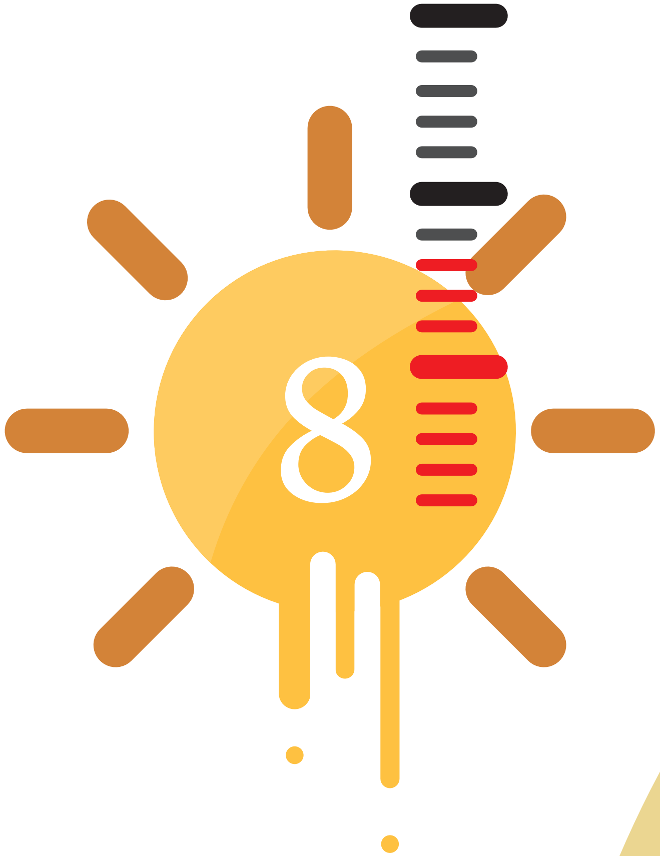
Knowledge about the human thermoregulation has increased considerably, as the topic is researched to a great extent over the last few decades. With this knowledge, thermal models and indices have been developed to simulate the physiological response of the human body in all possible thermal environments and are used to estimate heat stress and heat strain (11). However, often the thermal models and their information regarding heat stress and heat strain do not reach the general population, as these thermal models and indices are most of the time not publicly available and difficult to understand and use for the general population (273). Integrating these thermal models and indices into tools, such as a mobile application, combined with weather forecast data could be a solution to provide information regarding heat stress and heat strain in a user-friendly and understandable manner to the general population (273). The development and validation of such a mobile application, ClimApp, is described in *Chapter 6*. The output of ClimApp, the ClimApp index, is based on the WBGT and PHS and contains information about the estimated heat strain at that moment and the expected heat strain for the next 24 hours. Based on the level of estimated heat strain it provides advice to the user regarding hydration, clothing and rest. Results of this study show participants were positive about the user-friendliness of ClimApp, but did not think they would use ClimApp frequently and believed the information was irrelevant for them. This is in line with a recent study looking into the effectiveness of national heat plans, where care organisations were shown not to be familiar with heat policies and did not prioritize the heat (267). This is quite remarkable as the number of heat illness cases are increasing and the negative effects of heat occur in all populations exposing themselves to the heat. Therefore, there needs to be more focus on making people aware of the negative health risks in the heat. ClimApp could play a role as a tool to make heat warnings more accessible for everyone and make people aware of appropriate behaviour during periods with high ambient temperatures.

7.5. FUTURE DIRECTIONS AND PRACTICAL IMPLICATIONS

An important step into providing scientific-based information regarding thermal strain in a user-friendly way is made with the mobile application ClimApp. However, more research is needed to make this information more accurate on an individual level and increase relevance for vulnerable people. Greater accuracy in individual heat strain data will give better insights for individuals dealing with extreme heat to make changes both on a physiological as behavioural level, resulting potentially in a lower level of vulnerability. Combining epidemiological studies with lab and field studies is of great benefit. Vulnerable populations can be identified by epidemiological studies, as shown in *Chapter 4* that mortality amongst older women is higher than amongst older men in the Netherlands. Causes for higher level of vulnerability needs to be researched in lab and field studies. Once causes are known, precautionary measures can be conceptualized and included in heat policies.

Currently, the environmental thresholds, e.g. the environmental conditions where heat gain exceeds heat loss and body core temperature cannot be maintained at equilibrium, are unknown for characteristics such as body morphology, aerobic fitness, age and individuals with chronic health conditions. Furthermore, environmental thresholds for only a few different types of clothing are available. Similar studies as the research presented in *Chapter 3* should be performed for the characteristics mentioned above and different types of clothing. To our knowledge, only one study investigated environmental thresholds for older unacclimated females exercising at moderate intensity (274) and one study determined the maximum skin wettedness for untrained and trained individuals while acclimated and unacclimated to the heat using a similar ramp protocol as described in *chapter 3* (275). For comparison between studies it is important to keep as many physiological characteristics, study protocols and measurement methods similar. However, for determining the moment of reaching uncompensable heat stress it does not seem to be influenced by the method for measuring core temperature, as shown in *chapter 3*. Once the environmental thresholds for different subpopulations are known, thermal indices and models such as the WBGT and PHS can be updated and improved based on this information. Heat policies can include information more specifically focused on subpopulations identified as vulnerable and mobile applications such as ClimApp can provide information and advice focused more on the individual.

Furthermore, research focused on the effectiveness of precautionary measures and thermal behaviour is needed to improve heat policies. In *Chapter 5* we showed that humans are capable of adapting to the heat, but the underlying causes are unknown. Heat policies including the most effective measures to reduce heat stress and heat strain can potentially change behaviour and reduce the occurrence of heat-related morbidity and mortality. However, before people will change their behaviour and apply precautionary measures, people need to realise the severity of the risk heat can have for their health. In joint effort with children, elderly and patients with chronic diseases efforts should be undertaken to get a better understanding of the convictions driving thermal behaviour, so that heat strain mitigation strategies can be implemented successfully.



Chapter 8

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Dutch summary (Nederlandse samenvatting)

List of Publications

Acknowledgements

About the author

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8

DUTCH SUMMARY (NEDERLANDSE SAMENVATTING)

De klimaatverandering is een van de grootste uitdagingen van de 21e eeuw en is een grote bedreiging voor onze gezondheid. Temperatuurrecords worden steeds vaker gevestigd en hittegolven vinden frequenter plaats, zijn heviger en duren langer. De toenemende hitte heeft significante gevolgen voor alle populaties, maar in hevigere mate voor kwetsbare mensen of mensen die blootgesteld zijn aan de hitte tijdens werk of sport. Morbiditeit en mortaliteit nemen sterk toe tijdens periodes met extreme hitte, en zelfs als de striktste klimaatdoelen uit het Parijs-akkoord worden gehaald zal dit alleen maar verder toenemen.

Er zijn veel factoren die de kwetsbaarheid van mensen voor hitte-gerelateerde morbiditeit en mortaliteit beïnvloeden zoals meteorologische parameters, menselijk gedrag en fysiologische karakteristieken. Iedereen ondervindt de negatieve gevolgen van de hitte, maar deze kunnen verergerd of verminderd worden door het gedrag aan te passen. In welke mate gedrag aangepast moet worden is afhankelijk van fysiologische karakteristieken, aangezien mensen verschillen in hun gevoeligheid voor hitte.

Meteorologische parameters welke hittestress beïnvloeden zijn luchttemperatuur, luchtvochtigheid, windsnelheid en stralingstemperatuur. Deze meteorologische parameters samen gecombineerd in een thermische index of model kunnen een indicatie geven van de thermische omgeving waar een individu zich in bevindt. Zodra zo een thermische index of model ook gebruik maakt van fysiologische karakteristieken van het individu, kan er een preciezere indicatie worden gegeven van de ervaren hittestress. Fysiologische karakteristieken die invloed hebben op de ervaren hittestress zijn onder andere de lichaamssamenstelling, mate van hitte acclimatisatie, fysieke fitheid, leeftijd, geslacht en aanwezigheid van chronische ziektes. Deze thermische indices of modellen gecombineerd met fysiologische karakteristieken kunnen belangrijke waarschuwingen en informatie bevatten voor mensen die blootgesteld worden aan de hitte. Adviezen die de hittestress verminderen kunnen onder andere bestaan uit koelingsstrategieën, advies voor een rustperiode van een bepaalde duur of een bepaalde hoeveelheid vochtinname. In dit proefschrift ligt de voornaamste focus op de fysiologische karakteristieken geslacht en leeftijd, en hoe een mobiele applicatie, ClimApp, welke fysiologische karakteristieken combineert met meteorologische parameters en thermische indices en modellen, ingezet kan worden om advies te geven over hittestress voor de algemene bevolking.

Kinderen

Jonge kinderen (<5 jaar) zijn afhankelijk van ouders of verzorgers voor hun gezondheid en welzijn. Het thermoregulatiesysteem van kinderen is nog niet volledig ontwikkeld en samen met de afhankelijkheid van ouders of verzorgers maakt dat jonge kinderen kwetsbaar zijn voor hoge temperaturen. Omdat de meeste huishoudens tegenwoordig bestaan uit tweeverdieners, worden kinderen steeds vaker naar de kinderopvang gebracht. In kinderdagverblijven zijn de leid(st)ers verantwoordelijk voor het welzijn, en dus ook het thermisch comfort, van de kinderen. Het is belangrijk dat de leid(st)ers in een kinderdagverblijf kennis hebben van de thermoregulatie van een kind en de juiste voorzorgsmaatregelen nemen om het risico van hittestress te verminderen. De leid(st)ers moeten ook een goede inschatting kunnen maken van de thermische staat van het kind, aangezien de kinderen zelf vaak te jong zijn om aan te kunnen geven of ze het warm of koud hebben. Het belang hiervan neemt alleen maar toe sinds er steeds vaker hete dagen zich voor doen. Het is echter niet bekend of de leid(st)ers in staat zijn om een goede inschatting van de thermische toestand van kinderen te maken. Vandaar dat wij in *Hoofdstuk 2* hier onderzoek naar hebben gedaan. De huidtemperatuur van de kinderen is gemeten op vier locaties om een indicatie te krijgen van de thermische toestand. Vervolgens hebben de leid(st)ers een inschatting gemaakt van de thermische toestand van het kind en zijn ze geïnterviewd over hun kennis op het gebied van hitte en kinderen. Uit de resultaten van dit onderzoek blijkt dat het lastig is voor de leid(st)ers om een inschatting te maken van de thermische toestand van de kinderen. Daarnaast konden veel leid(st)ers niet aangeven wat voor symptomen een kind krijgt als het beroerd wordt van de hitte. Vooral onder de leid(st)ers met minder dan vijf jaar werkervaring op een kinderdagverblijf was het kennisniveau op het gebied van hitte en kinderen laag. Uit dit onderzoek is als advies gekomen dat leid(st)ers van kinderdagverblijven beter getraind moeten worden in hun thermische inschattingsvermogen en kennisniveau, vooral bij leid(st)ers met weinig werkervaring.

Geslacht

Geslachtsverschillen in thermoregulatie bestaan door verschillen in antropometrie, hormoonhuishouding en fysieke fitheid. Over het algemeen hebben vrouwen een lager lichaamsgewicht en lagere fysieke fitheid dan mannen, wat zorgt voor een snellere stijging van de kerntemperatuur tijdens inspanning op vergelijkbare intensiteit. Daarnaast zweten vrouwen minder dan mannen, wat voornamelijk tijdens extreme hitte en/of extreme inspanning resulteert in een verminderde capaciteit om warmte kwijt te raken. In *Hoofdstuk 3* hebben we onderzocht of er een verschil is tussen mannen en vrouwen wanneer er oncompenseerbare hittestress wordt bereikt. Oncompenseerbare hittestress houdt in dat bij een bepaalde omgevingsomstandigheid en inspanningsniveau de kerntemperatuur niet meer stabiel gehouden kan worden, en begint te stijgen. De resultaten van dit onderzoek laten zien dat als mannen en vrouwen op dezelfde intensiteit inspanning leveren bij dezelfde thermische omstandigheden, vrouwen eerder oncompenseerbare hittestress krijgen dan mannen. Hieruit blijkt dat vrouwen kwetsbaarder zijn voor de hitte dan mannen. Dit is in lijn met de resultaten van het onderzoek dat is beschreven in *Hoofdstuk 4*, waaruit blijkt dat er meer vrouwen sterven tijdens hitte dan mannen in Nederland. In dit onderzoek hebben we de dagelijkse sterftecijfers van 23 jaar in Nederland onderzocht aan de hand van de gemiddelde dagelijkse temperatuur. Hieruit blijkt temperatuur-gerelateerde sterfte zich voornamelijk voordoet onder ouderen, en dan voornamelijk de oudsten (>80 jaar oud). In deze groep ouder dan 80 jaar zien we ook het verschil in sterfte tijdens de hitte tussen mannen en vrouwen.

Ouderen

Zoals hierboven beschreven doet temperatuur-gerelateerde sterfte zich voornamelijk voor onder ouderen. Dit kan verklaard worden door het slechter functioneren van het thermoregulatie systeem, verminderde fitheid en toenemende prevalentie van chronische aandoeningen. Naarmate mensen ouderen worden, neemt de zweetproductie af en begint het zweten bij een hogere kerntemperatuur. Ook neemt de huiddoorbloeding af waardoor er minder warmte via de bloedvaten in de huid afgegeven kan worden naar de omgeving. Samen met de verminderde fitheid en de hogere incidentie van chronische aandoeningen bij ouderen zorgt dit voor een verhoogde kwetsbaarheid van ouderen in de hitte. Echter, in *Hoofdstuk 5* laten we zien dat ouderen zich wel degelijk kunnen aanpassen aan de hitte. In dit hoofdstuk hebben we aan de hand van de *Minimum Mortality Temperature (MMT)*, de gemiddelde landelijke omgevingstemperatuur waarbij het minste aantal dagelijkse sterfgevallen zich voordoet, en 23 jaar aan sterftedata van ouderen (>65 jaar oud) uit Nederland, laten zien dat de gevoeligheid voor hoge temperaturen over de jaren afneemt. Dit kan komen door fysiologische aanpassingen, gedragsveranderingen of verbeterde technologie en infrastructuur, echter is er meer onderzoek nodig om de daadwerkelijke oorzaak te achterhalen.

ClimApp

Thermische indices en modellen gecombineerd met fysiologische karakteristieken en weersvoorspellingen kunnen belangrijke waarschuwingen en adviezen geven aan mensen die blootgesteld worden aan de hitte. Zo'n hulpmiddel kan aangeboden worden in de vorm van een mobiele applicatie en ClimApp is hier een voorbeeld van. ClimApp heeft als doel wetenschappelijke informatie over hittestress makkelijker toegankelijk te maken voor de algemene bevolking. In *Hoofdstuk 6* wordt de ontwikkeling en validatie van ClimApp beschreven. ClimApp is gebaseerd op thermische indices en modellen en geeft informatie over de hittestress op dit moment en de verwachte hittestress in de komende 24 uur. Gebaseerd op de geschatte hittestress adviseert ClimApp de gebruiker over, onder andere, hydratatie, kleding en rustperiodes. Resultaten van dit onderzoek laten zien dat de deelnemers ClimApp gebruiksvriendelijk vonden, maar dat ze niet verwachten de mobiele applicatie vaak zelf te gebruiken en ze vonden de informatie irrelevant voor zichzelf. Dit is opmerkelijk aangezien er steeds meer mensen de negatieve gevolgen ondervinden van de hitte en dit voorkomt in alle populaties.

Conclusies en vervolgonderzoek

Met de onderzoeken beschreven in dit proefschrift is een stap gemaakt naar het individualiseren van adviezen tijdens hete periodes, met de focus op kwetsbare leeftijdsgroepen en geslacht, en hoe deze wetenschappelijk onderbouwde adviezen overgebracht kunnen worden naar de algemene bevolking. Meer onderzoek is nodig naar individuele fysiologische verschillen in de thermoregulatie om adviezen over ervaren hittestress verder te kunnen personaliseren. Daarnaast is meer onderzoek naar de meest effectieve methodes om hittestress tegen te gaan en wat mensen kunnen veranderen aan hun gedrag van grote relevantie.

List of publications

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ABOUT THE AUTHOR

Mireille Folkerts was born in Assen on September 14, 1990. After finishing highschool in Assen she studied Human Movement Sciences at the Rijksuniversiteit Groningen. In 2014 she finished the master with a major in motor function and cognition in healthy ageing. With a passion for climate change and ageing she started in October 2017 her PhD on the ClimApp project at the Vrije Universiteit Amsterdam. Sweden, Denmark and The Netherlands collaborated on the ClimApp project to develop an advanced mobile application integrating weather forecast data and individual characteristics into models to predict body responses, provide health risk warnings and advise regarding cold and heat stress. During her PhD Mireille conducted field studies, laboratory experiments and epidemiological analysis relevant for ClimApp.