On temperature-related mortality in an elderly population and susceptible groups

Daniel Oudin Åström
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En normal sanning varar i högst 20 år

Henrik Ibsen
Everything familiar has disappeared. The world looks brand-new.

Wonderful. It really snowed last night, isn’t it wonderful?

A new year, a fresh, clean start.

It’s like having a big white sheet of paper to draw on.

A day full of possibilities.

It’s a magical world, Hobbes. Oh, buddy...

Let’s go exploring!
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Jag ser verkligen, verkligen fram mot vår gemensamma vandring mot horisonten.
ABSTRACT

**Background:** Climate change has increased the frequency, intensity, duration, and spatial extent of some extreme weather events, for instance heat waves. Societies today are experiencing an ongoing change in the population structure yielding an increasing proportion elderly due to increased longevity, resulting in higher prevalence of chronic and degenerative diseases. Literature suggests that the elderly and certain susceptible subgroups with chronic disease are among the most vulnerable to heat waves and elevated temperatures.

**Aim:** The main aims of this thesis were to expand the scientific knowledge on the short-term effects of extreme heat on mortality for the general population and certain susceptible groups in society, to investigate the development of this relationship over time and to attribute mortality to observed climate change.

**Methods:** Daily numbers of deaths and daily meteorological observations during three different periods were collected for present day Stockholm County, Sweden. The analyses of the relationship between mortality and temperature extremes were analysed using a time series approach. The regression models assumed the daily counts of mortality to follow an overdispersed Poisson distribution and adjustments were made for time-trends as well as confounding factors.

**Results:** The literature review of recent studies identified a strong relationship between heat and heat waves and increasing death rates among the elderly, particularly for respiratory and cardiovascular mortality. A statistically significant increase in total daily mortality during heat extremes in all decades investigated, as well as over the entire period, during the period 1901-2009 with a declining trend over time for the relative risk associated with heat extremes, was reported in paper II. For the period 1901-2009 cold extremes significantly increased mortality, with a more disperse pattern over individual decades and no declining trend over time. Paper III attributed increased mortality due to climate change between 1900-1929 and 1980-2009. This increase was mainly due to a large number of excess heat extremes in the latter time period. Furthermore certain subgroups of the population above 50, were in paper IV found to have significantly increased mortality during heat waves as compared to non-heat wave days. Individuals diagnosed with Congestive Heart Failure, diabetes, psychiatric disorders as well as those surviving a myocardial infarction all had higher risk of dying on
a heat wave day compared to a non-heat wave day. This was the case for the general population above 50 as well.

**Conclusions:** Although the relative risk of dying during extreme temperature events appears to have fallen in Stockholm, Sweden, such events still pose a threat to public health. The elderly population and certain susceptible subgroups of the population experience higher relative risks of dying on heat waves days as compared to normal summer days. Some of the groups most susceptible during heat waves were identified. In order to minimize future impacts of heat waves on public health, identifying susceptible subgroups in an ageing society as well as develop strategies to reduce the impact of future temperature extremes on public health will be important.
SAMMANFATTNING

Effekterna av klimatförändringarna märks genom allt mer extrema väderförhållanden, till exempel värmeböljor. En värmebölja definieras ofta som en längre, sammanhängande period med temperaturer mycket över vad som är normalt för en region. Vämerelaterade dödsfall ses som det mest påtagliga hälsohotet med klimatförändringen i Sverige inom överskådlig tid.

Huvudsyftet med avhandlingen var att studera hur äldres dödlighet påverkas av höga temperaturer och att identifiera andra grupper i befolkningen som kan vara extra känsliga för höga temperaturer. Daglig information om antal döda och temperatur samlades in för Stockholms län och analyserades med hjälp av så kallad tidsserieanalys. Avsikten var att försöka svara på följande frågeställningar:

- har effekten av temperatur på dödlighet förändrats över tid i Sverige?
- kan förtida dödsfall i Stockholm tillskrivas klimatförändringar?
- vilka grupper i samhället löper en ökad risk att avlida i förtid under värmeböljor?

Resultaten visade att den ökade risken att dö under värmeböljor minskade över tid under 1900-talet. Resultaten visade också att antalet värmeböljor ökade under slutet av 1900-talet jämfört med början av 1900-talet, och att antalet döda på grund av värmeböljor därför ökade trots att risken att dö under värmeböljor minskade över tid. Resultaten visar också att äldre och kroniskt sjuka, till exempel diabetiker, har en ökad risk att avlida under värmeböljor jämfört med normala sommardagar.

Även om risken att avlida under en värmebölja minskat över tid, är värmeböljor fortfarande ett hälsoproblem, speciellt då dessa förväntas öka i antal och intensitet. Att i kommande studier identifiera ytterligare känsliga grupper samt att genomföra åtgärder som minskar effekterna av extrem värme på befolkningsnivå är, ur ett folkhällopspektiv viktigt.
## ABBREVIATIONS

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<tr>
<th>Abbreviation</th>
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<tr>
<td>AIC</td>
<td>Akaike Information Criterion</td>
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<tr>
<td>AT</td>
<td>Apparent Temperature</td>
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<tr>
<td>CHF</td>
<td>Congestive Heart Failure</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>df</td>
<td>degrees of freedom</td>
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<td>DT</td>
<td>Dew Temperature</td>
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<td>MAT</td>
<td>Maximum Apparent Temperature</td>
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<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
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<tr>
<td>NSC</td>
<td>No Susceptible Cohort</td>
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<td>MMT</td>
<td>Minimum Mortality Temperature</td>
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<td>RR</td>
<td>Relative Risk</td>
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<tr>
<td>RRR</td>
<td>Relative Risk Ratio</td>
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<td>T</td>
<td>Mean Temperature</td>
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OBJECTIVES

“Man, unlike anything organic or inorganic in the universe, grows beyond his work, walks up the stairs of his concepts, emerges ahead of his accomplishments.” —John Steinbeck

The main aims of this thesis were to expand the scientific knowledge on the short-term effects of extreme heat on mortality for the general population and certain susceptible groups in society, and to investigate the development of this relationship over time.

The specific objectives were the following:

To review the impact from exposure to heat and heat waves on the mortality and morbidity in the older adult population

To estimate the relative risk of dying on days defined as a temperature extreme on a decadal basis for the period 1901–2009 and to identify any trends in susceptibility over this time period

To propose a method to attribute mortality to observed climate change

To identify certain groups in society who are more susceptible than the general population during heat waves
This thesis is based on the following papers, which will be referred to by corresponding Roman numerals:


INTRODUCTION

The effects of temperature on mortality have been studied for centuries in Sweden; the seasonality of mortality was studied using parish registers already in the 1760s. Today the impacts of heat waves and high temperatures are studied all over the world, using modern epidemiological and statistical methods.

Different geographical locations will experience extreme temperatures relative to what is normal for that specific location. Thus extremely high temperatures in the study region (Stockholm, Sweden) will not be considered extreme in, for instance, a Middle Eastern climate, nor will the impact on mortality be the same at a given temperature across regions.

The large changes occurring in society during the 20th century, such as socioeconomic development, demographic and epidemiological transitions, and health system development, are all factors likely to affect heat related mortality on a population level. Moreover, with a changing climate the intensity and frequency of heat waves are increasing.

These fundamental changes made me interested in investigating the development of the sensitivity to temperature extremes over time. Thus, what started out as a research project into heat related mortality and susceptible groups in present day Sweden ended up also as an inquiry into modifications of heat susceptibility across the last century.
BACKGROUND

Climate change

“Climate is what we expect, weather is what we get.” —Mark Twain

Before addressing the issue of climate change, the reader should be familiar with the fact that weather and climate are measured using different time scales. Weather describes the meteorological conditions over a short time and includes such things as day-to-day variation. Climate is the average of daily weather observations over a longer period of time in a region. Climatological periods are often defined as time periods of at least 30 years to limit the influence of daily, yearly, and regional variability.

Temperature data from the last century indicate a shift towards higher ocean and land mean temperatures globally. These observed higher mean temperatures are likely due to both natural variability and human influence. The frequency of extreme events such as heat waves changes due to shifts in the distribution of these events. A heat wave is an episode of days with extremely high temperatures in relation to what is normal for a region.

During the last decade, which has likely been one of the hottest globally during the last millennia, the number of heat waves in Europe increased. The heat wave of 2003 in western Europe coincided with probably one of the hottest summers since the 1500s. The spatial extent and the temperatures noted during the heat wave of 2010 even surpassed this previously unprecedented event. There is an approximately 80% probability that the recorded temperatures of the 2010 heat wave would not have occurred without climate change. The scientific reasons for the observed increase in the number of extreme temperature events can be readily explained. With increasing average temperatures, the temperature distribution shifts upwards. More persistent and more severe heat waves are increasing at a faster rate than daily extreme temperatures, and further increases in the frequency, intensity, duration, and spatial extent of heat waves as well as continued increases in temperatures are projected for the future.

The health impacts of climate change can be divided into direct effects and effects that occur over time. Among the direct effects is exposure to an increasing number of heat waves, storms, wildfires, and floods. Indirect effects include changed distributions of infectious disease vectors and displacements of populations.
Urban Heat Island

The effect of high temperatures on the health of populations will likely be more pronounced in an urban area than a rural area due to, among other things, the phenomenon of urban heat islands. With an increasingly urbanised population and a projected increase in the number of heat waves, there is a need to investigate the effect of elevated temperatures in urban areas.

A heat island is an area with warmer temperatures than the surrounding areas. This phenomenon can occur anywhere, both in urban and in rural areas, but the surfaces in a city have more of the qualities needed to store and release heat. As a city becomes more densely urban, the buildings and infrastructure that cover the soil surface modify the atmosphere, which leads to changes in the climate of that area. Specifically, the roads and pavement in a city are made out of materials with low albedo, which means that the surface of these materials does not reflect away the rays from the sun. This is also true for most buildings. The result of this is higher temperatures on those surfaces and in the surrounding air. Furthermore, cities have less vegetation such as trees and plants, which helps reduce the temperature by creating shaded areas and by cooling the air by evapotranspiration. This phenomenon can take place in cities of all sizes, but the urban heat island effect usually decreases with the size of the city. Air pollutants from traffic and industries as well as waste heat from air conditioning and refrigerators also contribute to the creation of urban heat islands. Although urban heat islands can occur throughout the year, a negative effect on public health is more likely to appear in the summer. The ideal weather conditions for urban heat island formation, calm and cloudless days with elevated temperatures, most often occur during summer and autumn.

Additionally, many cities have narrow urban canyons with reduced sky view factors that tend to absorb and reemit the radiated energy from their surfaces. These canyons also alter the natural flow of air in the city, which further contributes to the urban heat island effect.

As illustrated in Figure 1 below, both night-time and daytime temperatures are higher in the urban and downtown areas than in the surrounding rural and suburban areas.
Epidemiological methods

The word “Epidemiology” is derived from the Greek Epi, “among”, and Demos, “people”. In modern language it can be defined as the science about description and causes of health (and disease) in any defined population. Causation is often difficult to assess however, and the Bradford Hill criteria from 1965 is still useful to consider when assessing causality\textsuperscript{14} (see appendix 1):

**Environmental Epidemiology**

Steenland and Savitz defined environmental epidemiology as: “Environmental epidemiology may be defined as the epidemiologic study of the health consequences of exposures that are involuntary and that occur in the general environment\textsuperscript{15}”. In such a setting causality may be tricky to assess due to typically small effects, difficulty in exposure assessment, and residual confounding.

To study the short term effect of temperature on mortality, we study how a population’s exposure varies over time. All individuals in Stockholm are assumed to have the same identical exposure to temperature at a certain time point. In epidemiology, this is denoted an ecological design, in contrast to individual level studies where exposure is assessed for each individual separately.

The limitations of assuming an identical exposure in time for a whole population is that there will in reality most certainly be differences within
cities and between individuals in terms of actual exposure. Exposure misclassification due to exposure measurement error does not, in linear models, bias the estimates, but rather reduces precision\textsuperscript{16}. The main advantage by investigating short-term effects in an ecological design is that individual characteristics do not change over time, and slowly changing factors can be controlled for using a smooth function\textsuperscript{17}. It is important to note that one of the most important methodological problems in epidemiological studies on individual level, are therefore not an issue here, namely bias due to residual confounding on an individual level.

In this thesis, Papers II, III and IV all makes use of a time series analysis approach to study the short term effect of temperature on mortality. The response variable used in these regression models, daily number of deaths, is a count variable assumed to follow an overdispersed Poisson distribution. Overdispersion occurs when the variance of the daily number of deaths is larger than the mean number of deaths occurring during the study period. In equation form, the association between the daily number of deaths and heat waves in Paper II-IV is modelled as:

\[
\text{Mortality}_t \sim \text{Poisson}(\mu_t) \\
\log(\mu_t) = \text{intercept} + \text{weekday} + \text{public holiday} + S(\text{trend, df=4/6 per year}) + \text{heat wave}
\]

\text{(1)}

Day of the week (weekday) was included in the model as a categorical explanatory variable and public Swedish holiday (public holiday) as a binary variable.

The relationship between extreme heat and mortality were studied over longer periods of time making it necessary to control long-term underlying changes of the mortality counts. These changes can be accounted to, as previously described, changes in population health and medical advancements. Furthermore mortality patterns occurring within years have to be taken into account. Such seasonality can reflect increasing mortality in winter due to, among other things, influenza. Adjusting for the underlying time trends that occur over longer periods, like seasons and years, should leave enough short term variation in the daily counts of mortality to be explained by other factors, like temperature extremes. Adjustments of these underlying time trends were, in papers II, III and IV made using a smooth function of time. These smooth functions were selected based on a trade-off between avoiding residual confounding and leaving enough variability in the
daily mortality counts to be explained by day to day variation in temperatures\textsuperscript{17}.

Effect modification is present when the factor, for instance, age groups and sex, modifies the causal relationship between the outcome and the mentioned factor. By performing stratified analyses of the temperature-mortality relationship the precision of the impacts of health is increased. This helps define vulnerable subgroups in order to reach them for protective and preventive approaches. To investigate whether the effect of exposure to extreme temperatures differs between sex and different age groups the analyses were stratified and a Relative Risk Ratio (RRR) calculated as the ratio between the RR of the group of interest and the RR from the reference group. Statistical significance was based on the calculated Z-score and corresponding p-values\textsuperscript{18}.

**Different temperature metrics**

A wide range of temperature metrics can be used when studying the impact of temperature on mortality and morbidity. Daily mean, maximum, and minimum ambient temperatures have been used in studies of temperature-related mortality. The daily mean temperature is derived from multiple observations during the day, which could result in a better exposure estimate. The two extreme points during a day, the minimum and maximum temperatures, are likely to affect mortality due to increased physiological pressure on the body. The minimum temperature during a day is often observed at night-time when physical activity is usually low. How well this minimum temperature corresponds to actual exposure can be questioned in a climate like Sweden’s, where people live in well-insulated houses, so the daily minimum temperature probably provides a poor estimate of actual exposure. The daily maximum temperature, on the other hand, usually occurs in the middle of the day when physical activity is normally higher.

Other weather conditions also might have an impact on the effect of hot and cold temperatures on mortality. For instance, a windy day will help reduce the effect of heat (if air temperatures are lower than skin temperatures) but increase the effect of cold. The apparent drawback of using ambient temperature as the exposure variable is that it likely differs from skin temperature, which is what signals the body to start regulating its own temperature when it is too high\textsuperscript{19}. Thermoregulatory effects, like evaporation, are reduced on a humid day. Therefore, incorporating humidity, which is based on the humidex\textsuperscript{20} and dew point, into the apparent temperature might be more appropriate. Apparent temperature (AT) is
calculated from the daily mean temperature (T) and the daily mean dew point temperature (DT) with the following formula\textsuperscript{21}:

\[
AT = -2.653 + 0.994^*T + 0.0153^*(DT)^2. 
\]  
(2)

The time series of meteorological data from Stockholm used for Papers II and III in this study is among the longest in the world. Temperature observations have been recorded daily at the old astronomical observatory since the 1750s. The temperature data used were reconstructed by Moberg et al. from the observational data\textsuperscript{22}. The observatory is presently situated in the city centre due to a strong urbanisation process that has been occurring in Stockholm since the mid-19\textsuperscript{th} century. This process of urbanisation has led to an artificial warming at the observatory by about 0.7°C on average\textsuperscript{23}. These data were normalised in order to account for the urban heat island effect at different times. In paper III, both the observed data and the normalised data when calculating the number of excess heat extremes were used.

**Temperature and mortality**

There is an extensive body of evidence for the impact that high and low ambient temperatures have on public health\textsuperscript{24,25}. In Sweden, parish records were used to study the seasonality of mortality in the 18\textsuperscript{th} century\textsuperscript{26}. Early English records provided evidence of excess winter mortality as well as an increase in mortality after cold spells\textsuperscript{27,28}.

**Demographical and epidemiological transition**

It is important to recognise that a number of indirect effects on mortality that have occurred during the 20\textsuperscript{th} century have influenced the temperature–mortality relationship as well as its development over time.

Life expectancy at the national level in Sweden increased from about 56 years during the first decade of the 20\textsuperscript{th} century to more than 81 years in 2009\textsuperscript{29}. Fundamental changes in public health and mortality also occurred during this period. Until the middle of the 20\textsuperscript{th} century, the large increase in human life expectancy at birth was largely due to the reduction in infant mortality. Over the course of the 20\textsuperscript{th} century, the impact of infectious disease decreased. The incidence and virulence of many infectious diseases is strongly dependent on temperature. The decline was apparent even before the introduction of effective medicines, vaccines, and treatments during the 1940s. However, subsequent developments have led to an almost negligible
role of infectious disease from the 1950s onward when antibiotics, vaccinations, and advancements in medical therapies began to change health standards\textsuperscript{30}. The period thereafter was instead dominated by chronic diseases, such as cardiovascular disease (CVD) and cancer, with death occurring in old age\textsuperscript{31}. Life expectancy still continues to increase, with improvements in the survival rate of the older adult population.

The trend in the association between short-term mortality caused by weather conditions and adaptation to regional ambient temperatures has been observed in a few studies of historic registers. Carson et al. (2006) used daily mortality and temperature data for London, England\textsuperscript{32} and Ekamper et al. (2009) used daily data on morality and temperature for Zeeland, the Netherlands\textsuperscript{33}. Both studies reported declining vulnerability to temperature-related mortality across the 20th century. Davis et al. reported decadal declines in annual heat-related mortality rates in the United States from 1964 to 1998\textsuperscript{34} and Lerchl (1998) found declining amplitude of the seasonality of mortality in Germany from 1946 to 1995\textsuperscript{35}. The reported declines in the United States and Germany were due to, among other things, increased use of air conditioning, central heating and improvements in the public health sector.

\textit{Temperature – mortality relationship}

The temperature-mortality relationship has been described as a J or U-shaped curve, with a temperature at which mortality is at a minimum\textsuperscript{36}-\textsuperscript{40}. Minimum mortality temperature (MMT) varies greatly across countries and regions ranging from a daily mean temperature of 10-12°C in Scandinavian countries\textsuperscript{41,42} to 27°C in Miami\textsuperscript{36}.

MMT also could be affected by changing demography, particularly an increased proportion of elderly in the population. The expected increase in the number of older adults and other potentially vulnerable groups, both in absolute numbers and as a proportion of the population, could make the impact of temperature extremes on human health more severe\textsuperscript{43} because the older and chronically ill populations are more sensitive to temperature-related mortality\textsuperscript{25}. For example, increasing effects of heat on mortality have resulted in a lower MMT on a population level in Spain, which can be explained by an increasingly large population of vulnerable individuals\textsuperscript{44}. 
Physiology of temperature related mortality

Heat

When exposed to high ambient temperatures, the human body must dissipate the heat load in order to maintain a body temperature of 37°C. This process is called thermoregulation. The body regulates its interior temperature by increasing the heart rate and cardiac output to redistribute blood to the skin where heat is dissipated and by increasing sweating. Sweating results in the loss of water and salt, which will impair the body’s thermoregulatory functions if not replenished45.

The negative effects of heat and heat waves on human health range from relatively mild symptoms, such as heat syncope and fainting, to more serious symptoms, such as cramps, heat exhaustion, and heat stroke46. One of the physiological mechanisms that triggers heat-related mortality is the increased stress on the heart and lungs from the thermoregulatory process, and chronically ill and older people are particularly susceptible to this47. Mortality reported as due to heat stroke is not very common in Sweden; most deaths are reported as due to cardiovascular disease. Losing water and salt from sweating causes haemoconcentration, which in turn can cause thrombosis. Coronary and cerebral thrombosis accounts for a large number of deaths during heat waves.

Cold

The large number of excess winter deaths reflects the fact that seasonal factors have a substantial impact on the common causes of death. As is the case with heat, winter deaths are seldom attributed directly to cold exposure, and very few deaths are recorded as due to hypothermia.

Cardiovascular diseases, such as ischaemic heart disease and cerebrovascular disease, account for about half of all excess cold-related mortality. The underlying physiological mechanism induced by cold exposure that causes these fatalities is that the body slows down blood flow to the skin in order to preserve heat. This in turn leads to thrombosis due to haemoconcentration. Furthermore, increased levels of red blood cell counts and plasma cholesterol during cold exposure can be thrombogenic. The other half of cold-related deaths is caused by respiratory diseases. These diseases are more widespread during winter because people spend more time indoors in crowded places and because the cold negatively affects the
immune system. These deaths are often due to pneumonia resulting from a common cold or infection\textsuperscript{48}.

**Timing of heat related deaths**

The effect of heat on health is usually a direct effect, meaning that the negative impacts on health are closely related in time to the onset of a heat wave. Mortality increases are noted the same day or one or two days after the onset of a heat wave\textsuperscript{49,50}, and high mortality rates persist throughout the length of the heat wave\textsuperscript{51}.

The effect of exposure to cold on health is usually spread out over a longer time period. Cold-related mortality has been reported after much longer time lags than for heat. A study of weather-related mortality in the US found an impact on mortality from cold temperatures using an average of the effects from same-day exposure and from exposure up to 25 days earlier\textsuperscript{50}.

It has been reported that the effect of heat early in the season has a higher impact on mortality than heat later in the season when the general population, and the susceptible groups in particular, have had time to adapt to increasing temperatures\textsuperscript{52}. An ageing population is of special importance because it increases the size of the susceptible population. In Italy this increase in the number of older adults could help explain the increased effect of high temperatures early in the summer period when the size of the susceptible population is greater\textsuperscript{53}.

Although increased mortality during heat waves was reported in a study in the UK, Kovats et al. (2004) did not find that hospital admissions increased to the same extent. This might be due to the fact that the time lag from the onset of heat-related symptoms to death is rather short such that death usually occurs outside of hospitals\textsuperscript{54}.

**Mortality displacement**

A reduction of mortality following a heat wave have been observed in a number of studies \textsuperscript{55,56}, Zhang et al (2014) reports mortality displacement in China for hot but not for cold temperatures\textsuperscript{57}. The increases in mortality during a heat wave were compensated for by lower than normal mortality during the days, or weeks, following a heat wave. This suggests that older adults and people with chronic disease, who generally would have been expected to die soon after the heat wave anyway, are most affected by elevated temperatures.
**Adaptation**

Individuals can adapt to heat and cold through behavioural and physiological changes. Among behavioural changes are living in better-insulated houses and using air conditioning. A US study reported that inhabitants in cities where a high percentage of homes had air conditioning were less susceptible to extreme temperatures, but this tended to be related to temperature because warmer summers correlated to the wider use of air conditioning\(^37\). The body physiologically adapts to higher than normal temperatures through increased sweating and improved cardiovascular capacity\(^58\).

The impacts of heat and cold are region specific, with heat-related mortality occurring at higher temperatures in warmer regions\(^50\). A study of 50 US cities found that inhabitants living in cities with milder summers were more susceptible to heat than inhabitants in cities with higher summer temperatures. Also, the density of the population was associated with elevated risk of death; thus, a less sprawling city is more vulnerable\(^37\). The importance of air conditioning was found in another study in the US where higher mortality was associated with not having an air conditioner\(^59\).

**Susceptible groups**

In order to effectively implement preventive measures such as heat warning systems and organizational changes in the health sector during heat waves, it is important to identify the groups most susceptible to extreme heat and heat waves\(^60\). In this section, we explain how these susceptible groups are affected by extreme temperatures and describe the protective and preventive measures that can be taken.

Epidemiological studies investigating the effect of heat on vulnerable groups have consistently shown that heat waves and high ambient temperatures affect the elderly population to a greater degree than the younger population. However, the evidence for other groups is more difficult to interpret. For example, many studies have shown that women are affected by heat more than men, but a few other studies have found no such difference. It is important to keep in mind that the epidemiological evidence does not always reach consensus.
**Age**

Numerous studies have provided evidence that the elderly population, in most studies defined as the population above 65 years of age, is among the most susceptible groups. Kovats and Hajat (2008) reported a larger effect on mortality in the older adult population. Mortality due to heat waves and elevated ambient temperatures increases with age according to Basu and Samet (2002) and Basu (2009). They reported an increased risk of death associated with increased age above approximately 50 years. Kenny et al. (2010) added to the evidence of mortality among the elderly. Ye et al. (2012) found a significant short-term effect from elevated temperatures on morbidity among the population above 65 years old. Kravchenko (2013) also reported the elderly population to be more susceptible.

The body’s thermoregulatory abilities decrease with age, which contributes to most of the negative impacts from elevated temperatures on the health of older adults. Many older adults also have chronic diseases and impaired abilities to undertake proper proactive measures to cool themselves or their homes.

Increased mortality and morbidity during heat waves is not only a problem in the older ages, but also in the earlier stage of life. A study in US found high mortality rates (7.3 per 100,000) among the 45-54 year olds. Another study performed in the US reported a statistically significant increase in the risk of dying for infants during their first year of life per 10 °F increase in mean daily apparent temperature. Elevated risk (although not significant) was also seen for children under 5 years old. A recent study of eastern and southern Mediterranean cities found increased vulnerability among the young populations, which constitutes a major public health problem because of the increase in years of life lost.

**Sex**

The evidence that sex modifies the effect of heat on mortality is contradictory. Numerous studies have analysed men and women separately, and both sexes have been shown to be more vulnerable than the opposite sex. Women have been reported to be affected more often than men, however.

In England and Wales, women above 65 years old were significantly worse off during a heat wave than the men. In California no difference was found between women and men, whereas in Ontario, Canada women had
elevated risks of dying during times of elevated temperature. In Paris during the 2003 heat wave, an increased risk of heat-related death was observed for unmarried men but not for unmarried women, and a protective effect of being a foreigner was observed in women but not in men.

In Italy, women had a higher risk of dying on a 30 °C day relative to a 20 °C day than men. A higher risk was also observed among widows and widowers. Women in Australia were shown to be more vulnerable than men during times of elevated temperature. Contrasting results were found in the 45-64 year old population in Madrid, Spain where the men had higher risk of dying than the women. This difference might be due to differences in life expectancy between men and women because many of studies do not adjust for differences in age.

**Respiratory disease**

The evidence for an increased sensitivity to elevated temperatures among persons with respiratory diseases such as asthma or chronic lung disease is quite extensive. A substantial number of studies have reported an association between heat waves/high ambient temperatures and increased mortality and/or morbidity due to respiratory causes. In England and Wales higher risks of dying for those with respiratory disease have been reported. A recent study in the US found that increased risk of hospitalisation of older adults for respiratory diseases was associated with increases in daily temperature and that the risks were higher in cooler counties.

A Chinese study reported that a 1°C increase in the 4-day moving average for diurnal temperature range was found to be associated with a 1.25% increase in daily chronic obstructive pulmonary disease (COPD) mortality. Increased risk of dying has also been reported on cold days. Rocklöv et al reported increasing odds of death among COPD patients in Stockholm Sweden. Schwartz (2005) speculated that when exposed to extreme cold a COPD patient, whose lungs typically are colonised by bacteria, is more prone to respiratory infection.

**Cardiovascular disease**

Extensive epidemiological evidence for an increased susceptibility to elevated temperatures has also been reported for those with cardiovascular disease. As with respiratory disease, an extensive number of studies have reported an association between high temperature/heat waves and increased
mortality and/or morbidity from cardiovascular disease\textsuperscript{25,61,62,75-77}. A meta-analysis by Turner et al. (2012)\textsuperscript{76} suggested that the impacts of elevated temperatures on cardiovascular morbidity were smaller and had higher variation across studies than the impacts found in studies focusing on mortality.

An extensive review of studies that focused solely on the relationship between high temperature and myocardial infarction (MI) showed that 7 out of 13 studies reported a relationship between elevated temperatures and a statistically significant increased risk of heart attack\textsuperscript{82}. In England and Wales temperatures above a regional threshold were associated with increased mortality due to MI\textsuperscript{77}. Specifically for Sweden, increased odds of dying for survivors to MI have been reported in Stockholm\textsuperscript{80}, whereas a decrease of hospitalizations due to acute MI with increasing temperatures was found in Gothenburg\textsuperscript{83}.

Cerebrovascular disease has been found to be associated with increased risk of death when temperatures are elevated\textsuperscript{67,84}. A five-city study performed in China for four different climatic zones found that increased mortality due to cerebrovascular disease was associated with low temperatures but not with high temperatures\textsuperscript{57}.

**Diabetes**

People with diabetes also have an increased risk of dying during heat waves. A statistically significant increased risk of dying among diabetics on a hot day has been reported\textsuperscript{37,81}, but the physiological mechanisms behind this increased risk of dying among diabetics are not fully understood. Schwartz (2005)\textsuperscript{81} speculated that the increased risk of dying might be due to the combined effect of the increased stress on the circulatory system due to elevated temperatures and impaired autonomic control and endothelial functions.

**Neurological disorders**

A history of psychiatric disorders has been associated with a higher risk of dying of heat-related causes\textsuperscript{70,75,84,85}. Furthermore, depression, psychiatric disorders, and circulatory disorders of the brain were found to significantly increase the risk of dying on a 30 °C day relative to a 20 °C day in another study performed in Italy\textsuperscript{70}. Individuals with diseases of the central nervous system, such as Alzheimer disease and dementia, have been found to be more susceptible to extreme heat\textsuperscript{86}.  
A study of the relationship between daily temperature and daily suicide counts in England and Wales detected an increased risk of suicide during hot weather. Above 18°C there was an increase in suicide and violent suicide\textsuperscript{87}.

Certain medications, especially diuretics and psychotropic drugs have been found to be associated with increased susceptibility to high temperatures\textsuperscript{61,88}. A study of the 2003 heat wave in France found an increased risk of death for people above 70 years old who were taking antidepressants or antipsychotic drugs during the heat wave. Anxiolytic drugs were found to reduce the risk of death during the heat wave\textsuperscript{89}.

**Socio-economy and ethnicity**

Black people and less-educated people were found to have a larger risk of heat-related death than other groups in a study of four US cities, probably because they were more likely to be living in areas with a low prevalence of air conditioners\textsuperscript{59} A study of 11 cities located in the eastern US found that poverty, higher altitude, and lack of air conditioners increased the risk of dying from extreme temperatures\textsuperscript{36}. Differences in mortality in the US have also been reported on a zip-code level\textsuperscript{86}.

No evidence that deprivation modifies the risk of temperature-related death has been found in England, Wales\textsuperscript{65} and Australia\textsuperscript{72}. Furthermore, living alone, living in a flat, and ethnicity did not modify the effects of heat\textsuperscript{65}. In contrast, living alone or living on the top floor was found to contribute to heat sensitivity\textsuperscript{90}. For the population over 55 years old in Paris, the excess mortality rate was twice as high during heat waves in the most deprived cantons versus the least deprived cantons\textsuperscript{91}. Living in a low-income area in Italy was found to modestly increase the risk of dying during elevated temperatures\textsuperscript{70}.

Negative effects of belonging to a vulnerable social group have been reported in the US\textsuperscript{36}, but significant evidence that socioeconomic differences modify the risk of dying during heat waves has not been reported for Europe\textsuperscript{65}. Low incomes do, however, increase the probability of belonging to other vulnerable populations known to modify the risk of heat-related mortality. These risk groups include people with chronic diseases, obese people, and people residing in substandard housing\textsuperscript{61}. 
Increased dependency

Kovats and Hajat (2008)⁶¹, Hajat et al (2010)⁸⁸ Martiello and Giacchi (2010)⁷⁴ reported evidence of increased vulnerability to heat extremes when the level of frailty and dependency is increased. Hospitalised patients⁸⁴, patients residing in nursing homes⁶⁵,⁹¹ and patients confined to bed⁷⁵ all have an increased risk of dying on days with temperatures above a certain threshold. Mortality during heat waves was investigated for nursing home patients in Germany, and an increase in the daily ambient maximum temperature above a threshold of 26 °C was associated with an increased mortality rate⁹². Nursing home residents were found to be vulnerable in England and Wales as well⁶⁵. In Italy, older hospitalised patients were reported to face an increased risk of dying on days with a mean temperature of 30 °C as compared to a day with 20 °C, and a history of psychiatric disorders or cerebrovascular disease were associated with a higher risk of death⁸⁴. Heat extremes increase the risk of death among people with impaired health status, the risk also increases with the degree of dependence⁶¹,⁷⁴,⁸⁸.

Working population

Increasing temperatures also affect the working population and lead to more work-related injuries. In Australia, increasing maximum temperatures were associated with increases in daily injury claims for a number of occupations⁹³.

Protective factors

Fortunately, heat-related mortality and morbidity are preventable, and some protective measures can be taken at both the societal and individual levels. At the individual level, a number of factors that can reduce the impact of heat on health have been reported, including having air conditioning in the home and visiting places that have air conditioning. Having access to a social network and to transportation was also found to be protective against heat-related mortality and morbidity⁶²,⁷⁵.
MATERIALS AND METHODS

“Essentially, all models are wrong but some are useful” - George E.P. Box

Paper I

The first paper reviewed the impact of heat waves and elevated temperatures on mortality and morbidity among the older adult population. Even though a number of reviews on the impacts of elevated temperatures and heat waves on population health have been published, until presently none focused entirely on older adults. Furthermore, there has been a rapid increase in the number of studies published on this specific topic in recent years.

The studies included in the review were published in English between 1 January 2008 and 31 December 2010. The studies were identified by a PubMed search, using the following key words: heat wave, mortality, morbidity, elderly, and temperature. To be considered for inclusion, the following criteria had to be met:

1. The relationship between high temperature and mortality and/or morbidity was studied.

2. The results were specific for the older adult population. If this group was analysed as a subpopulation, only the results corresponding to older adults were included.

The results included were presented as a relative increase in deaths, hospitalisations, or emergency room visits per degree Celsius above a predetermined threshold or as the RR in mortality or morbidity corresponding to heat wave days as compared to a non-heat wave days.

The review did not strictly follow one specific definition of a heat wave because the RR reported in the included studies often used local definitions of a heat wave. However, a typical characteristic of a heat wave was the occurrence of daily temperatures over several consecutive days above a threshold defined as an extreme temperature percentile. This threshold varied greatly across countries and regions.

Paper II

The aim of the second paper was to investigate the mortality related to high and low temperature extremes from the beginning of the 20th century until
the present day in Stockholm, Sweden, stratified by sex and age. These two factors have been previously shown to modify the effect of temperature on mortality.

Table 1. Descriptive statistics for mortality data

<table>
<thead>
<tr>
<th>Decade</th>
<th>Mean</th>
<th>Std</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>Total</th>
<th>0-14</th>
<th>15-65</th>
<th>65+</th>
<th>65-79</th>
<th>80+</th>
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<tbody>
<tr>
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<td>16.7</td>
<td>4.8</td>
<td>16</td>
<td>3</td>
<td>40</td>
<td>54781</td>
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<td>41.51</td>
<td>29.33</td>
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<td>8.69</td>
</tr>
<tr>
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<td>6.0</td>
<td>16</td>
<td>3</td>
<td>60</td>
<td>62517</td>
<td>20.82</td>
<td>45.48</td>
<td>33.70</td>
<td>22.44</td>
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</tr>
<tr>
<td>1920-29</td>
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<td>4.6</td>
<td>14</td>
<td>3</td>
<td>39</td>
<td>52814</td>
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<td>44.22</td>
<td>43.15</td>
<td>28.51</td>
<td>14.64</td>
</tr>
<tr>
<td>1930-39</td>
<td>16.9</td>
<td>5.3</td>
<td>16</td>
<td>3</td>
<td>44</td>
<td>61691</td>
<td>6.96</td>
<td>41.62</td>
<td>51.42</td>
<td>35.17</td>
<td>16.24</td>
</tr>
<tr>
<td>1940-49</td>
<td>22.1</td>
<td>6.4</td>
<td>22</td>
<td>6</td>
<td>53</td>
<td>80763</td>
<td>5.80</td>
<td>37.28</td>
<td>56.92</td>
<td>36.63</td>
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</tr>
<tr>
<td>1950-59</td>
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<td>29</td>
<td>13</td>
<td>54</td>
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<td>30.90</td>
<td>64.98</td>
<td>42.12</td>
<td>22.86</td>
</tr>
<tr>
<td>1960-69</td>
<td>35.3</td>
<td>6.8</td>
<td>35</td>
<td>14</td>
<td>63</td>
<td>128806</td>
<td>3.07</td>
<td>28.13</td>
<td>68.80</td>
<td>41.94</td>
<td>26.87</td>
</tr>
<tr>
<td>1970-79</td>
<td>39.1</td>
<td>7.1</td>
<td>38</td>
<td>20</td>
<td>72</td>
<td>142637</td>
<td>1.86</td>
<td>26.07</td>
<td>72.07</td>
<td>40.79</td>
<td>31.29</td>
</tr>
<tr>
<td>1980-89</td>
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<td>7.2</td>
<td>41</td>
<td>20</td>
<td>81</td>
<td>150221</td>
<td>1.25</td>
<td>20.48</td>
<td>78.27</td>
<td>39.57</td>
<td>38.70</td>
</tr>
<tr>
<td>1990-99</td>
<td>42.2</td>
<td>7.4</td>
<td>42</td>
<td>22</td>
<td>75</td>
<td>154181</td>
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<td>16.39</td>
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<td>48.45</td>
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<tr>
<td>2000-09</td>
<td>42.4</td>
<td>7.1</td>
<td>42</td>
<td>20</td>
<td>70</td>
<td>154993</td>
<td>0.65</td>
<td>15.79</td>
<td>83.56</td>
<td>27.03</td>
<td>56.53</td>
</tr>
</tbody>
</table>

Daily numbers of deaths from all causes (Table 1) as well as daily mean temperatures (Table 2) were collected for the period 1901–2009 for present day Stockholm County, Sweden. Heat extremes were defined as days for which the 2-day moving average of mean temperature, Lag01, was above the 98th percentile. Cold extremes were defined as days for which the 26-day moving average of mean temperature, Lag025, was below the 2nd percentile. Daily data were collected for the entire period (Model 1, 1901–2009) as well as by decade (Model 2) to take into account increasing temperatures over time. The RRs for mortality during heat and cold extremes were calculated for both models.
Table 2. Descriptive statistics for temperature data

<table>
<thead>
<tr>
<th>Decade</th>
<th>Summer Mean ± (Lag 01)</th>
<th>Max (Lag 01)</th>
<th>Winter Mean ± (Lag 025)</th>
<th>Min (Lag 025)</th>
<th>N Heat Extremes (98th percentile) N Cold Extremes (2nd percentile) Decadal 98th percentile for Heat Extremes (N) Decadal 2nd percentile for Cold Extremes (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1901-09</td>
<td>15.14 °C</td>
<td>25.30 °C</td>
<td>-2.19 °C</td>
<td>-7.05 °C</td>
<td>55 (20.80 °C) 11 (-6.93 °C)</td>
</tr>
<tr>
<td>1910-19</td>
<td>15.51 °C</td>
<td>24.35 °C</td>
<td>-2.28 °C</td>
<td>-8.32 °C</td>
<td>66 (20.80 °C) 55 (-6.93 °C)</td>
</tr>
<tr>
<td>1920-29</td>
<td>15.08 °C</td>
<td>24.45 °C</td>
<td>-2.31 °C</td>
<td>-2.19 °C</td>
<td>44 (20.80 °C) 64 (-6.93 °C)</td>
</tr>
<tr>
<td>1930-39</td>
<td>16.74 °C</td>
<td>25.80 °C</td>
<td>-0.82 °C</td>
<td>-5.41 °C</td>
<td>79 (20.80 °C) 4 (-6.93 °C)</td>
</tr>
<tr>
<td>1940-49</td>
<td>16.58 °C</td>
<td>26.70 °C</td>
<td>-3.50 °C</td>
<td>-13.20 °C</td>
<td>91 (20.80 °C) 0 (-6.93 °C)</td>
</tr>
<tr>
<td>1950-59</td>
<td>16.13 °C</td>
<td>25.65 °C</td>
<td>-2.20 °C</td>
<td>-10.73 °C</td>
<td>55 (20.80 °C) 53 (-6.93 °C)</td>
</tr>
<tr>
<td>1960-69</td>
<td>16.27 °C</td>
<td>24.25 °C</td>
<td>-2.89 °C</td>
<td>-11.15 °C</td>
<td>51 (20.80 °C) 119 (-6.93 °C)</td>
</tr>
<tr>
<td>1970-79</td>
<td>16.62 °C</td>
<td>27.70 °C</td>
<td>-1.60 °C</td>
<td>-10.22 °C</td>
<td>66 (20.80 °C) 89 (-6.93 °C)</td>
</tr>
<tr>
<td>1980-89</td>
<td>16.15 °C</td>
<td>26.90 °C</td>
<td>-2.56 °C</td>
<td>-11.93 °C</td>
<td>58 (20.80 °C) 158 (-6.93 °C)</td>
</tr>
<tr>
<td>1990-99</td>
<td>16.95 °C</td>
<td>26.95 °C</td>
<td>-0.25 °C</td>
<td>-7.01 °C</td>
<td>113 (20.80 °C) 22 (-6.93 °C)</td>
</tr>
<tr>
<td>2000-09</td>
<td>17.46 °C</td>
<td>25.30 °C</td>
<td>-0.55 °C</td>
<td>-7.27 °C</td>
<td>126 (20.80 °C) 10 (-6.93 °C)</td>
</tr>
</tbody>
</table>

The mortality–temperature relationship was studied using a time series approach that assumed the daily counts of mortality followed an overdispersed Poisson distribution and to which a generalised linear model was fit. Holidays, pandemics, completeness of data, and day of week were included in the models as binary and categorical explanatory variables. Furthermore, the time trends in the daily number of deaths over the period were described by a smooth function that used approximately 4 degrees of freedom per year. The large change in the population at risk over the 110 years was included in the smooth function, along with other slowly time-varying extraneous factors.

To investigate the effects of sex and age, the analyses were stratified and the RRR was calculated as the ratio between the RR of the group of interest and the RR of the reference group. To investigate any time trends in the RRs, bearing in mind the substantial difference in standard errors of the RR estimates over time, a weighted least squares linear regression with the RR estimate as the dependent variable and decade as the independent variable using the weights inversely proportional to the variance of each RR was performed.

**Paper III**

The aim of Paper III was to propose a new method to attribute extreme temperature-related mortality to observed changes in climate between two different 30-year time periods.
The time period from 1900 to 1929 was used as the baseline for identifying the temperatures corresponding to the 2nd and 98th percentiles for cold (Lag025) and heat (Lag01), respectively. These temperatures were then used to determine the number of excess heat and cold extremes during the period from 1980 to 2009 (Table 3). The numbers of excess temperature extremes were then used to attribute mortality during temperature extremes to the change in the frequency of these extremes.

Table 3. Descriptive statistics for temperature data adjusted for urban heat island effect

<table>
<thead>
<tr>
<th>Decade</th>
<th>Mean (Lag 01)</th>
<th>Summer Mean (Lag 01)</th>
<th>Max (Lag 01)</th>
<th>Mean (Lag025)</th>
<th>Winter Mean (Lag 025)</th>
<th>Min (Lag 025)</th>
<th>N Heat Extremes</th>
<th>N Cold Extremes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1900-1909</td>
<td>5.48 °C</td>
<td>15.14 °C</td>
<td>25.30 °C</td>
<td>5.48 °C</td>
<td>-2.73 °C</td>
<td>-8.01 °C</td>
<td>76 (19.6 °C)</td>
<td>43 (-6.32 °C)</td>
</tr>
<tr>
<td>1910-1910</td>
<td>5.84 °C</td>
<td>15.51 °C</td>
<td>24.35 °C</td>
<td>5.85 °C</td>
<td>-2.57 °C</td>
<td>-8.67 °C</td>
<td>87 (19.6 °C)</td>
<td>89 (-6.32 °C)</td>
</tr>
<tr>
<td>1920-1929</td>
<td>5.60 °C</td>
<td>15.08 °C</td>
<td>24.45 °C</td>
<td>5.57 °C</td>
<td>-2.69 °C</td>
<td>-9.45 °C</td>
<td>57 (19.6 °C)</td>
<td>88 (-6.32 °C)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1900-1929</td>
<td>5.64 °C</td>
<td>16.58 °C</td>
<td>26.70 °C</td>
<td>5.63 °C</td>
<td>-2.66 °C</td>
<td>-9.45 °C</td>
<td>220 (19.6 °C)</td>
<td>220 (-6.32 °C)</td>
</tr>
<tr>
<td>1980-1989</td>
<td>5.80 °C</td>
<td>15.20 °C</td>
<td>25.90 °C</td>
<td>5.80 °C</td>
<td>-3.37 °C</td>
<td>-12.70 °C</td>
<td>83 (19.6 °C)</td>
<td>189 (-6.32 °C)</td>
</tr>
<tr>
<td>1990-1999</td>
<td>6.72 °C</td>
<td>16.00 °C</td>
<td>26.05 °C</td>
<td>6.84 °C</td>
<td>-1.05 °C</td>
<td>-7.94 °C</td>
<td>139 (19.6 °C)</td>
<td>49 (-6.32 °C)</td>
</tr>
<tr>
<td>2000-2009</td>
<td>7.28 °C</td>
<td>16.51 °C</td>
<td>24.30 °C</td>
<td>7.29 °C</td>
<td>-1.35 °C</td>
<td>-7.94 °C</td>
<td>156 (19.6 °C)</td>
<td>13 (-6.32 °C)</td>
</tr>
<tr>
<td>Attribution period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980-2009</td>
<td>6.60 °C</td>
<td>15.91 °C</td>
<td>26.05 °C</td>
<td>6.61 °C</td>
<td>-1.93 °C</td>
<td>-12.70 °C</td>
<td>378 (19.6 °C)</td>
<td>251 (-6.32 °C)</td>
</tr>
</tbody>
</table>

Mortality was attributed to climate change by calculating the number of excess deaths ($M_E$) due to extreme events using the following formula:

$$M_E = \Delta EE \times M_B \times (RR_{EE} - 1),$$  \hspace{1cm} (3)

where $\Delta EE$ is the difference between the number of extreme events occurring in 1980–2009 and in 1900–1929, $M_B$ is the seasonal baseline mortality for 1980–2009, and $(RR_{EE} - 1)$ is the increase in risk during every excess extreme event estimated from the 1980–2009 mortality data.

The increase in risk of death during a temperature extreme was estimated for the population in 1980–2009 using a similar time series approach as in Paper II. The seasonal baseline mortalities were calculated for the winter months of January, February, and March as well as the summer months of June, July, and August.
Furthermore, whether the number of cold and heat extremes occurring during a year influenced the RR of mortality to investigate adaptation to more frequent temperature extremes over the last 30 years was determined. For this purpose, linear regression with the yearly RR of mortality as the independent variable and the number of extremes occurring the same year as the dependent variable was used.

**Paper IV**

The aim of Paper IV was to identify cohorts of patients with increased susceptibility during heat waves in Sweden and Italy. Susceptible cohorts were selected based on a literature search. Comparisons of mortality during heat waves among the susceptible cohorts with specific diagnoses, identified from the general population above 50 years of age were made. In order to increase contrast and to identify any specific susceptible cohorts that could be driving mortality during heat waves, the non-susceptible (NSC) group from the general population that did not belong to any of the susceptible cohorts was included.

**Table 4 Descriptive statistics of the cohorts in Rome and Stockholm**

<table>
<thead>
<tr>
<th>SIZE OF COHORT</th>
<th>MORTALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ROME COHORT</strong></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>17668</td>
</tr>
<tr>
<td>COPD</td>
<td>17235</td>
</tr>
<tr>
<td>DIABETES</td>
<td>49233</td>
</tr>
<tr>
<td>MI</td>
<td>7045</td>
</tr>
<tr>
<td>PSYCHIATRIC</td>
<td>22837</td>
</tr>
<tr>
<td>NSC</td>
<td>1011766</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1106511</td>
</tr>
</tbody>
</table>

| **STHLM COHORT** |            |
| CHF              | 20463      |
| COPD             | 3811       |
| DIABETES         | 16955      |
| MI               | 5591       |
| PSYCHIATRIC      | 11012      |
| NSC              | 465232     |
| TOTAL            | 512964     |

*Note. CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, MI = myocardial infarction, NSC = non-susceptible.*
Descriptive statistics for the total population above age 50 and for each of the investigated susceptible cohorts for two cities are presented in Table 4. Rome is the main city in Italy with approximately 2.7 million residents, whereas Stockholm has approximately 1.3 million residents. The percentage of the overall population older than 50 years is approximately 42% in Rome and 40% in Stockholm.

After a selection process based on different temperature metrics and Akaike Information Criteria (AIC) for the models, a heat wave day was defined as two consecutive days with temperatures exceeding the 95th percentile of maximum apparent temperature (MAT) in summers. A delayed effect of heat was incorporated by allowing the two days following a heat wave day to be heat wave days. The 95th percentile was calculated using daily temperature observations for the summer months (May, June, July, August, and September) for 1995–2008.

Table 5 Descriptive statistics for temperature data.

<table>
<thead>
<tr>
<th></th>
<th>MEAN</th>
<th>STD</th>
<th>MIN</th>
<th>MAX</th>
<th>95th percentile</th>
<th>N Heat Waves</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROME Tappmax</td>
<td>29.5</td>
<td>4.5</td>
<td>15.9</td>
<td>40.2</td>
<td>36.2</td>
<td>57</td>
</tr>
<tr>
<td>STHLM Tappmax</td>
<td>18.6</td>
<td>4.7</td>
<td>3.1</td>
<td>31.4</td>
<td>26.6</td>
<td>61</td>
</tr>
</tbody>
</table>

Temperature data for both cities are presented in Table 5. The definition of a heat wave, the 95th percentile of MAT, was 36.2 °C in Rome and 26.6 °C in Stockholm. The range of MAT was between 15.9 °C and 40.2 °C in Rome and between 3.1 °C and 31.1 °C in Stockholm. During 2000–2008, Rome experienced 57 heat wave days ranging from 0 in 2004 to 16 in 2006. Stockholm had a total number of 61 heat wave days, ranging from 0 in 2000 to 13 in 2006.

The mortality–heat wave relationship was investigated assuming that the daily number of deaths followed a Poisson distribution and a generalised additive model was fit. The approach in Paper IV is similar to the methods used for deriving RR estimates in Papers II and III. The yearly time trends throughout the period were handled differently, however, and were described by a cubic spline with six fixed degrees of freedom each year (doy). The variable doy is a count variable equal to 1 on May 15, 2 on May 16, and so forth on a yearly basis.
To investigate differences between age and sex as well as between groups, the RRR was calculated as the ratio of the RR of one cohort to the RR of the reference cohort. Statistical significance was determined by the calculated Z-score and corresponding p-values.

Trends in the mortality RR over time by year were investigated by including an interaction term with year and heat wave in the model. Furthermore, the period before, 2000–2002, and the period after, 2005–2008, the European heat wave of 2003 was investigated in order to determine whether any changes in the estimates of mortality could be detected following such an extreme event.
RESULTS

Paper I

In paper I, an increased risk of mortality and morbidity among the elderly was reported almost consistently throughout the literature as well as globally. Studies with mortality as an outcome were more common than studies reporting morbidity outcomes. Some differences between morbidity and mortality studies regarding the direction of results were also found, possibly because morbidity is limited to the number of hospital beds available. The morbidity studies usually focused on hospitalisations, and the associations reported for morbidity might not be as valid as those reported for mortality. This might be due to the availability and quality of the data as well as an apparent ceiling effect from the number of beds available as well as publication bias because negative results are harder to publish. Furthermore, much of the out-of-hospital morbidity likely results in mortality due to short lead times from the onset of increasing temperatures to mortality and is thus reported as mortality.

Certain subgroups of the older adult population were also identified as having increased risk of dying during heat waves, in addition to the fact that they already belong to a group more susceptible to the negative effects of heat on health. The two main groups were persons with respiratory and cardiovascular diseases. No consistent evidence for sex modifying the effect of heat was found, but women’s risks were reported as higher than men’s in a number of studies.

Additionally, the effects of urban heat islands on heat-related mortality and morbidity were mostly missing in the literature.

Paper II

The number of heat extremes increased over the course of the 20th century with a drastic increase during the last two decades investigated. A trend over time in the number of cold extremes was not apparent and varied by decade.

In Figure 1, the RRs and 95% confidence intervals (CI) of mortality during heat and cold extremes are shown for each decade as well as for the entire period (Model 1). The estimated effect of being exposed to extreme heat was generally higher than the estimated effect of being exposed to extreme cold.
For heat extremes, we report increased risk of dying on an extremely hot day versus a normal summer day during each decade as well as over the entire period. For the entire period, the risk of death during heat extremes increased by 10% (95% CI [8%, 13%]) and 12% (95% CI [10%, 14%]) for Models 1 and 2, respectively. A significant decline in RR estimates over the course of the 20th century was detected. For days defined as cold extremes compared to normal winter days, the risk of death increased by 6% (95% CI [3%, 8%]) and 4% (95% CI [2%, 5%]) over the entire period for Models 1 and 2, respectively. The decadal associations were more variable, and with even a protective effect of extreme cold found during the 1950s. A declining trend over time was also found, although this was not statistically significant. During the last three decades, the effect of extreme temperatures seemed to level off, and the decadal estimates were similar.

When stratifying the analyses similar trends for men and women as well as for different age groups were found. No strong evidence was found to suggest that age or sex modifies the effect of heat or cold.

**Paper III**

In Figure 2, a substantial shift in the temperature distributions towards warmer temperatures for both summer and winter is shown. During the
reference period 1900–1929, the 2nd and 98th percentile temperatures were –6.3°C and 19.6°C, respectively. Based on the 2nd/98th percentiles, during the period 1900-2009, there were 220 days defined as extreme temperature days. During the period 1980-2009 the number of cold extremes was found to be 251, yielding 31 excess days of extreme cold temperatures as compared to the baseline period of 1900-2009. A substantial increase in the number of days with extreme heat was found; these days occurred 378 times in the period 1980-2009, resulting in 158 excess days with extreme heat. The ranges of occurrence of temperature extremes per year were 0-57 for cold extremes and 1-38 for hot extremes.

From the time series Poisson regression models, there was a 5.6% (95% CI [2.9%, 8.2%]) increase in mortality during extreme cold days as compared to normal winter days. During days defined as extreme heat days, there was a 4.6% (95% CI [2.6%, 6.7%]) increase in mortality as compared to normal summer days.

The RR estimates during days with extreme heat and extreme cold remained stable over the period 1980–2009 in a decade-by-decade comparison (β_{trend cold} = 0.0063, 95% CI [−0.043, 0.056]; β_{trend heat} = 0.0077, 95% CI [−0.024, 0.039]) adjusting for general time trends of mortality for the total population. No short-term adaptation to more frequent temperature
extremes was found on a year-to-year basis because the number of temperature extremes occurring each year did not affect the RR estimates during heat and cold extremes. For heat, as well as cold, the relationship between the RR and the number of heat extremes occurring each year was slightly negative and non-significant ($\beta_{\text{heat extremes}} = -0.0033$, 95% CI $[-0.0066, 0.00091]$; $\beta_{\text{cold extremes}} = -0.0003$, 95% CI $[-0.0023, 0.0017]$). Thus, any new temperature extreme would be assumed to cause the same magnitude of additional mortality independently of the number of such events occurring over a year.

Using Formula 2 resulted in 288 excess premature deaths attributed to more frequent heat extremes during 1980–2009 and 75 excess premature deaths attributed to more frequent cold extremes.

**Paper IV**

In paper IV increased risks of dying during heat waves as compared to normal summer days were reported among certain susceptible groups in society in Rome, Italy and Stockholm, Sweden. In Rome, a day defined as a heat wave compared to a normal summer day increased the risk of dying for all investigated groups, although not significantly for the MI cohort. The same relationship was found in Stockholm with increased risks of dying during heat waves, albeit not significantly for the COPD and NSC cohorts.

In Rome, the RR during heat waves for the different cohorts ranged from 1.07 (95% CI [0.83, 1.39]) for the MI cohort to 1.25 (95% CI [1.10, 1.42]) for the COPD cohort. No significant differences between the NSC cohort and any other cohort were found, which suggests similar impacts of heat waves among the cohorts in the population of those 50 years or older. In Stockholm, the RR was lowest for the NSC cohort, 1.03 (95% CI [0.97, 1.08]), and highest for the psychiatric cohort, 1.28 (95% CI [1.07, 1.52]). The NSC cohort differed with borderline significance from the congestive heart failure, diabetes, and MI cohorts and differed significantly from the psychiatric cohort.
Figure 3 presents the RR and 95% CI associated with mortality during heat wave days compared with non-heat wave days by city for each of the investigated groups.

Age did not seem to be an effect modifier for any cohort in either city. The only cohort affected by age was the total population in Rome, where the population aged 75 years or older was more susceptible than those aged 50–74 years. Women were more vulnerable than men in the diabetes and NSC cohorts as well as in the total population in Rome. In Stockholm, men were more vulnerable than women in the COPD cohort and the total population.

No evidence of a trend over time in the yearly city-specific RR estimates for any cohort was found. When comparing the periods before and after the heat wave of 2003, contrasting patterns between the two cities were detected. In general, decreased vulnerability among the different cohorts in Rome was found, whereas in Stockholm increased estimates of susceptibility were found. Even though the differences are not statistically significant over the relatively short time period, it is a trend worth noticing.
DISCUSSION

In Paper I, increasing risks of mortality and morbidity among the elderly in almost all references in the literature were reported. The two main groups were persons with respiratory and cardiovascular diagnoses. Kovats et al (2004) reported contrasting patterns in mortality and morbidity and found only a small impact from high temperatures on hospital admissions and cardiovascular disease for older adults and a negative impact for cerebrovascular disease.

Another finding was that older adults in Britain are aware of the negative aspects of elevated temperatures and heat waves on their health and that they take actions to reduce the impact as well as recognise the risk in other older adults. The majority of the people interviewed did not consider themselves to be elderly or to belong to a risk group. In Australia, older adults reduced their risk by altering their behaviour. The majority of the people interviewed said that they had taken preventive actions to limit the impacts of heat based on previous experience. Furthermore, older adults in Australia with previous medical conditions such as cardiovascular conditions were more likely to self-report illness during heat waves, women more so than men.

In Papers II and IV, no strong evidence of sex modifying the effect of heat on health were found, even though generally in the literature women are reported to have higher risks. This increase in risk might be because women, on average, live longer and are thus more vulnerable due to a number of reasons such as increased age and social isolation. One might speculate that the small differences in risk of dying during heat extremes are due to the rather homogenous mortality patterns between men and women in Sweden.

The main finding of Paper II is the declining vulnerability to both hot and cold temperature extremes. Although the decline for cold is not statistically significant, there is an apparent tendency of reduced vulnerability. The results of two models were presented, since using the same cut-off temperature throughout the study period does not take into account an increasing temperature over time, which was known to have occurred during the study period, or acclimatization within decades. Consequently, the results might be biased upwards in the earlier decades because we might have estimated mortality in the steeper section of the temperature-mortality relationship slope. Given the large changes in society that took place over the
course of the 20th century, with unprecedented medical and technological developments as well as large demographic and epidemiological changes, it is of interest to study such a long time series in order to investigate whether the temperature–mortality relationship is stationary over time. The unusually long time series collected and used in Paper II allows the detection of possible impacts on public health from shifts in medical and technological advancements as well as changes in public health policies. In addition, the study of this development over the 20th century makes it possible to confirm results from studies that focused on shorter periods. These reported declines in vulnerability might have resulted from better dwellings, adaptation to weather extremes on an individual as well as a societal level, and the continuous improvements in the health care sector. However, it may not be appropriate to assume that historic trends will continue, with or without climate change.

Papers II, III, and IV all have methodological similarities with the same strengths and limitations. One apparent drawback is the ecological approach used. For these papers, data were collected from a single station assumed to represent temperature exposure for all of Stockholm County. Using temperature data from these fixed sites rather than using exposure data on the individual level can result in exposure measurement bias.

The same exposure to extreme temperature might differ at an individual level throughout the population due to the different adaptive measures taken. Indoor temperatures seem more accurately associated with heat perception than outdoor temperatures; thus, the subjective feeling of heat strain might not accurately reflect measured temperature. Furthermore, indoor and outdoor temperatures are poorly correlated due to a number of modifying factors. Assuming the same exposure within a city could lead to over- or underestimation of the risk of dying during heat waves. Hondula et al. (2013) found changing death rates within Philadelphia County in the US suggesting that identification of high-risk areas within a city is important from a public health perspective.

Heat waves were defined using an indicator variable where days with temperatures above a cut-off temperature were defined as heat wave days. The definition of a heat wave used in Papers II and III was the 98th percentile of mean daily temperature. Similarly, cold spells were in Papers II and III defined as days with temperatures below the 2nd percentile of mean daily temperature. The definitions were selected using all daily observations for the period 1901–2009, as well as on a decadal basis, to take into account increasing temperatures over time. In Paper IV, a heat wave day was defined as one of at least two consecutive days with temperatures exceeding the 95th
percentile of the maximum apparent temperature. To allow for a delayed effect of heat, the two days following a heat wave day were also considered to be heat wave days. To calculate the cut-off percentile, daily temperature observations for the summer months from the period 1995–2008 were collected.

These percentiles were selected arbitrarily because there is presently no scientific consensus on how to define a heat wave. A heat wave will occur at lower temperatures in a colder climate such as Sweden’s than in a warmer climate\(^{36}\). Given the large differences in temperature thresholds throughout the globe, percentiles are recommended rather than absolute temperatures. Montero et al (2013)\(^{99}\) argued that because it is impossible to establish a definition of a heat wave based on a fixed temperature or percentile that would be representative throughout the globe, region-specific percentiles are preferred. Typically, specific threshold temperatures associated with severe negative impacts on health should be identified regionally and used to define a heat wave. The choice of temperature metrics used in our papers – mean temperature and MAT – should not have too much of an impact on the derived risk estimates for different decades and vulnerable groups. Barnett et al. (2010) found strong correlation between different temperature metrics and concluded that, on average, they were equally suitable\(^{100}\).

Furthermore, Papers II, III, and IV all compared the risk of dying on an extremely hot or cold (Papers II and III) day compared to normal days. With MMT being reported at approximately the 60\(^{th}\) percentile in Sweden during 1980–2009 (Oudin Åström et al., forthcoming), reporting only the effect on mortality of heat waves using the 95\(^{th}\)/98\(^{th}\) percentiles means the effect of temperature on mortality might be underestimated. Applying similar reasoning regarding the cut-off temperatures in Paper III, we may have underreported the number of deaths due to cold and heat.

The demographics of the investigated areas must also be taken into consideration when comparing effects between regions. Increasing age of the population can be a driver of mortality at lower temperatures. Miron et al (2008)\(^{44}\) and Montero et al (2012)\(^{101}\) presented evidence that mortality starts to increase at lower temperatures in populations with a larger share of elderly in the population.

Papers II, III, and IV all investigated the short-term effects of exposure to extreme temperatures, and this is what is usually reported in the literature. However, Zanobetti et al. (2012) studied the impact of yearly temperature variability on mortality using a Cox proportional hazard approach and found
higher estimates of the hazard ratios among older adults and certain susceptible cohorts. They concluded that long-term increases in temperature variability might increase the risk of dying in these groups\textsuperscript{102}.

To attribute mortality to climate change in Paper III, the risk estimate was derived from a 30-year period, a standard approach in climate studies. The number of heat waves occurring on a yearly basis did not influence the RR estimate nor could a trend over time in the RR estimates be detected. Gou et al (2012)\textsuperscript{103} investigated the mortality risks among the elderly associated with high temperatures and found that main and added effects varied yearly, and years with high heat-related mortality were followed by years with low mortality. A summer, or winter, with high mortality depletes the size of the susceptible population, which possibly explains some of the observed patterns\textsuperscript{104-106}. This suggests that the same temperature exposure will have different impacts different years.

An added effect of heat wave duration has been reported in addition to heat intensity\textsuperscript{51,107}. A recent study separated the risk during elevated temperature into a “main effect” due to independent effects of daily high temperatures and an “added effect” due to duration of the heat wave. This added heat wave effect was found to occur only after a 4-day duration of the heat wave and was rather small compared to the main effect\textsuperscript{107}. Duration of heat waves was not considered when estimating mortality, however, and the approach taken here corresponds to the estimates from an average duration above the defined threshold. In Sweden, the additional effect of heat waves on mortality was previously investigated. This added effect of heat wave duration was found to yield excess mortality in the range of 8\%–11\% per heat wave day\textsuperscript{108}. By including the heat wave effect it is possible that precision of the mortality estimates would increase. Analysis of changes in the number of extreme events did not take into account changes in the intensity of these events. Barnett et al (2012) reported increasing risks for more extreme heat waves but no increase for cold spells\textsuperscript{109}. Therefore, the effect of heat extremes on mortality might have been underestimated.

Ambient temperature is usually controlled for when studying the impacts of air pollution on health. The correlation between temperature and some specific air pollutants such as ozone is well known\textsuperscript{110}, as is the fact that air pollution and temperature are both associated with mortality. A growing number of studies have investigated the confounding effects of air pollutants in temperature time series studies of mortality and morbidity\textsuperscript{76,85}. Analitis et al (2014) found the impact of heat waves on mortality to be higher on days with increased levels of air pollutants and argued that lack of adjustments for
ozone and PM$_{10}$ overestimates the effect of heat\textsuperscript{111}. Buckley (2014) however, argued that adjusting for air pollution when investigating the effects of temperature on health should be practised with caution and that any adjustments, if used, should be thoroughly justified\textsuperscript{112}. The rationale for not adjusting is that air pollution is more of a mediator than a confounder, for instance, ozone might be caused by heat waves.

The more susceptible population groups during times of elevated temperatures were discussed in this study, and societies are facing new challenges in helping these susceptible groups during hot days and heat waves. In a climate such as Sweden’s, heat awareness is generally low. Some of the measures that can be taken to avoid heat wave-related deaths are implementing heat warning systems and emergency plans, identifying areas with large susceptible populations, having more effective and readily available means of being able to cool oneself, and improving the care supplied to susceptible groups. In an increasingly urban world, a more conscious city design would relieve some of the effects of heat caused by urban heat islands\textsuperscript{113}. Susceptibility factors might also be different in different populations. The investigation of these factors among the younger and older adult populations would help target prevention activities to reduce the adverse effect of heat on health for different groups. A heat susceptibility indicator has been developed in Italy to identify older adults at risk during heat waves and is currently being used for local prevention activities\textsuperscript{114}. Gasparrini et al (2012) on the other hand, argued that targeting specific vulnerable groups based on their pre-existing disease would not be an efficient action in preventing mortality, because mortality in their study was due to a number of causes\textsuperscript{77}.

**Future research**

The rather limited availability of literature on the subjective perceptions of heat and elevated temperatures as well as the contrasting findings of Abrahamson et al (2009)\textsuperscript{94} and Hansen et al (2014)\textsuperscript{95} merits further inquiries. By designing questionnaires and targeting elderly and other susceptible groups as well as relevant stakeholders and employees in the care sector in a Sweden would help the design of heat warning systems nationally.

There is a growing body of studies where variation in temperature is being used as the exposure metric with interesting outcomes\textsuperscript{115, 116, 117}. It would be of interest to carry out such a study in a northern climate such as Sweden’s.
When assessing the short-term effects of heat waves on mortality Tong et al (2012) compared a time series approach to a case cross over approach and found the estimates to be consistent and comparable. Studying susceptible groups, especially groups with rare diseases where the daily mortality is low, reduces the statistical power in a time series approach, and thus we might not be able to detect certain susceptible groups. Therefore, analyses using a case crossover design could help identify susceptible groups by increasing the precision of the estimates.
CONCLUSION

Days with extremely hot (and cold) temperatures influence mortality rates even in a colder climate such as Sweden’s. Some subgroups in society are more vulnerable when being exposed to heat waves than the general population. A review of the literature identified the elderly population as a group consistently reported to have increased risks of dying during heat waves as compared to normal summer days. Furthermore, heat wave related mortality among certain susceptible cohorts was compared to “healthy” persons (NSC). For many of our cohorts we found that the RRs of mortality during heat waves differed from the NSC cohort.

Using daily mortality and weather data spanning more than a century declining vulnerability to extreme heat and cold in Stockholm were detected. Paper II is one of only a few papers using such data and thus is able to investigate trends over longer periods of time, this in a century characterized by change.

Proposing a novel approach extreme temperature-related mortality was attributed to observed climate change between the periods 1900-1929 and 1980-2009. The attributed number of deaths was mainly driven by an almost doubling of the number of heat extremes.
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APPENDIX 1

Bradford Hills criteria for assessing causality:

1. **Strength**: A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.

2. **Consistency**: Consistent findings observed by different persons in different places with different samples strengthen the likelihood of an effect.

3. **Specificity**: Causation is likely if a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.

4. **Temporality**: The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).

5. **Biological gradient**: Greater exposure should generally lead to greater incidence of the effect. However, in some cases, the mere presence of the factor can trigger the effect. In other cases, an inverse proportion is observed: greater exposure leads to lower incidence.

6. **Plausibility**: A plausible mechanism between cause and effect is helpful (but Hill noted that knowledge of the mechanism is limited by current knowledge).

7. **Coherence**: Coherence between epidemiological and laboratory findings increases the likelihood of an effect. However, Hill noted that "... lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations".

8. **Experiment**: Occasionally it is possible to appeal to experimental evidence.

9. **Analogy**: The effect of similar factors may be considered.
About the author:
To me, travelling is one of life’s best adventures. When the opportunity came to work with Professor Bertil Forsberg’s research group at Umeå University, I found myself on a journey 1250 km north to study heat. In a small cabin by the coast, “at the brink of civilisation”, as one of my friends put it, my first winter was a record cold one which I spent dwelling into heat-wave health effects. As the light arrived with the lovely Nordic summer, I was deeply into connecting my own world of demography with new concepts of environmental epidemiology. When I do not ponder on such things as how to combine 100-year old data records with modern epidemiological methods, I enjoy reading the odd Steinbeck novel, watching football, or spending time with my family and friends. While I’m now back in southern Sweden, I will always cherish the years up north for two things: that I was set free to roam in this inspiring research area, and that my most dearly beloved son was born there.